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KUNFIDENZJALI

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Komunikazzjoni diretta lill-Professjonisti tal-Kura tas-Saħħa -

dwar l-assoċjazzjoni ta' anagrelide hydrochloride (Xagrid® 0.5 mg) ma' riskju kardjovaskulari f'pazjenti bi trombożitemja essenzjali (TE)

Għażiż Professjonist fil-Qasam tal-Kura tas-Saħħa,

Komunikazzjoni dwar l-assoċjazzjoni ta' anagrelide hydrochloride (Xagrid® 0.5 mg kapsuli ibsin) ma' riskju kardjovaskulari f'pazjenti bi trombożitemja essenzjali (TE), tkun xi tkun l-istorja medika jew il-kundizzjoni medika tal-pazjent, u nota biex tiftakar li anagrelide hu indikat bħala terapija sekondarja f'pazjenti f'riskju.

Sommarju

Wara evalwazzjoni tal-avvenimenti kardjaċi kollha rrappurtati f'pazjenti taħt il-50 sena kkurati b'anagrelide, sezzjoni 4.4 'Twissijiet speċjali u prekawzjonijiet għall-użu', is-sezzjoni kardjovaskulari tas-Sommarju tal-Karatteristiċi tal-Prodott (SmPC) ta' Xagrid ġiet rinforzata.

Żdiedet dikjarazzjoni li tiddikjara li avvenimenti avversi kardjovaskulari serji jistgħu jseħħu f'pazjenti mingħajr mard tal-qalb issuspettat u b'eżami kardjovaskulari normali qabel il-kura.

Iż-żieda ta' din id-dikjarazzjoni lill-SmPC ta' Xagrid ma tibdilx il-benefiċċju/riskju kurrenti ta' anagrelide fil-kuntest tal-indikazzjoni terapewtika tiegħu bħala kura sekondarja f'pazjenti li huma f'riskju ta' trombożitemja essenzjali (ET).

Il-komunikazzjoni ta' din l-informazzjoni ġiet maqbula mal-Aġenzija Ewropea għall-Mediċini u l-Awtorità Dwar il-Mediċini ta' Malta.

Informazzjoni addizzjonali fuq it-tħassib li hemm dwar is-sigurtà

Dan l-aħħar, bħala parti ta' sorveljanza li għadha għaddejja, Shire wettqet evalwazzjoni tal-avvenimenti kardijaċi kollha rrappurtati f'pazjenti ta' inqas minn 50 sena kkurati b'anagrelide. Avvenimenti avversi kardjovaskulari serji seħħew f'dawn il-pazjenti iżgħar mibgħar ebda mard tal-qalb issuspettat, eżamijiet kardjovaskulari normali ta' qabel il-kura u mard majeloproliferattiv ikkontrollat. Dan wassal għar-rinfurzar tat-twissija kardjovaskulari f'Sezzjoni 4.4 'Twissijiet speċjali u prekawzjonijiet għall-użu' tal-SmPC tal-UE.

Ukoll, fl-istess sezzjoni tal-SmPC tal-UE, il-lista ta' avvenimenti avversi kardjovaskulari serji tkabbret biex tkun tinkludi kardjomijopatija u arritmiji kardijaċi, biex tkun konsistenti mas-sommarju tabulat ta' avvenimenti avversi (Sezzjoni 4.8). It-tibdil hu muri bl-aħmar hawn taħt, u għandu sinjal taħtu.

Twissijiet speċjali u prekawzjonijiet għall-użu

Kardjovaskulari

Avvenimenti avversi kardjovaskulari serji li jinkludu kardjomijopatija, kardjomegalija, insuffiċjenza konġestiva tal-qalb u arritmiji kardijaċi, ġew irrappurtati (ara sezzjoni 4.8).

Anagrelide għandu jintuża b'kawtela f'pazjenti ta' kull età b'mard tal-qalb magħruf jew issuspettat. Flimkien ma' dan, avvenimenti avversi kardjovaskulari serji seħħew ukoll f'pazjenti mingħajr mard tal-qalb issuspettat u b'eżami kardjovaskulari normali qabel il-kura.

Anagrelide għandu jintuża biss jekk il-benefiċċji potenzjali tat-terapija jegħlbu r-riskji potenzjali.

Anagrelide hu impeditur ta' AMP phosphodiesterase III ċikliku u minħabba l-effetti inotropiċi pożittivi tiegħu, eżami kardjovaskulari qabel il-kura (li jinkludi investigazzjoni addizzjonali bħal ekokardjografija, elettrokardjogramma) hu rakkomandat. Waqt il-kura, il-pazjenti għandhom jiġu mmonitorjati għal evidenza ta' effetti kardjovaskulari li jistgħu jeħtieġu iktar eżamijiet u investigazzjonijiet.

Informazzjoni addizzjonali dwar ir-rakkomandazzjonijiet lil professjonisti fil-qasam tal-kura tas-saħħa

Il-Professjonisti fil-Qasam tal-Kura tas-Saħħa huma mfakkra li l-pazjenti għandhom jiġu mmonitorjati qabel u matul il-kura għal evidenza ta' effetti kardjovaskulari li jistgħu jeħtieġu eżami kardjovaskulari u investigazzjoni addizzjonali. Dan sabiex jiġu osservati kwalunkwe effetti kardjovaskulari possibbli u tinbeda kura adattata lil pazjenti.

Xagrid huwa indikat biex inaqqas l-għadd għoli tal-plejtlets f'pazjenti li jkunu f'riskju ta' trombożitemja essenzjali (ET) li ma jittolerawx it-terapija attwali tagħhom jew li l-għadd għoli tal-plejtlets tagħhom ma jitnaqqasx għal-livell aċċettabbli bit-terapija attwali tagħhom.

Pazjent bi trombożitemija essenzjali li jkun f'riskju huwa ddefinit b'waħda jew aktar mill-karatteristiċi li ġejjin:

- 'il fuq minn 60 sena jew
- għadd tal-plejtlets > 1000 x 10^9/l jew
- passat mediku ta' reazzjonijiet trombo-emorraġiċi.

Sejħa għar-rappurtaġġ

Jekk jogħġbok irrapporta kwalunkwe avvenimenti avversi li jġarrbu l-pazjenti tiegħek li jkunu qed jieħdu anagrelide. Meta tirrapporta, jekk jogħġbok ipprovdi informazzjoni kemm jista' jkun, li tinkludi informazzjoni dwar l-istorja medika, kwalunkwe mediċina li tittieħed fl-istess ħin, id-data tal-bidu tal-marda u d-dati tal-kura.

Avvenimenti avversi għandhom jiġu rrappurtati.lill-:
Awtorità Dwar il-Mediċini/Post-licensing Directorate, 203, Level 3, Rue D' Argens, Gzira GZR 1368, MALTA, Formoli tar-rappurtaġġ u informazzjoni jinsabu fuq http://www.medicinesauthority.gov.mt/pub/adr.doc Kuntatt lokali: email: postlicensing.mru@gov.mt, Nru. tat-telefon (00356) 23439000 fax (00356) 23439161.

Avvenimenti avversi tal-mediċina għandhom jiġu rrappurtati wkoll lil Shire:-
Permezz ta' e-mail lil: GlobalPharmacovigilance@shire.com

Numru tal-fax: +44 1256 894715

Jekk ikollok kwalunkwe mistoqsijiet, jekk jogħġbok ikkuntattja lid-Dipartiment tal-Informazzjoni Medika ta' Shire

L-avvenimenti avversi għandhom jiġu rrappurtati wkoll lil Shire Pharmaceuticals Ltd fuq 01256 894000 jew lil Vivian Corporation Ltd. on +356 – 21320338/21344610/21344616 or pv@viviancorp.com"

Detentur tal-Awtorizzazzjoni għat-Tqegħid fis-Suq

Shire Pharmaceutical Contracts Limited
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Chineham, Basingstoke
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RG24 8EP
United Kingdom.

Dejjem tiegħek,

Dr. Birgitt Gellert
Viċi President Sorveljanza Medika u
Persuna Kkwalifikata Ewropea għal Farmakoviġilanza

Dr. Kristine Paridaens
Direttur Internazzjonali Mediku

Dokumenti Annessi

Kitba tal-SmPC(s) rivedut bit-tibdil highlighted

SOMMARJU TAL-KARATTERISTIĊI TAL-PRODOTT

1. ISEM IL-PRODOTT MEDIĊINALI

Xagrid kapsula iebsa ta' 0.5 mg.

2. GĦAMLA KWALITATTIVA U KWANTITATTIVA

Kull kapsula iebsa fiha 0.5 mg anagrelide (bħala anagrelide hydrochloride).

Eċċipjenti
Kull kapsula iebsa fiha lactose monohydrate (53.7 mg) u anhydrous lactose (65.8 mg).

Għal-lista kompluta ta' eċċipjenti, ara sezzjoni 6.1.

3. GĦAMLA FARMAĊEWTIKA

Kapsula iebsa.

Kapsula iebsa bajda matta li fuqha hemm stampat S 063.

4. TAGĦRIF KLINIKU

4.1 Indikazzjonijiet terapewtiċi

Xagrid huwa indikat biex inaqqas l-għadd għoli tal-plejtlets f'pazjenti li jkunu f'riskju ta' trombożitemija essenzjali (ET) li ma jittolerawx it-terapija attwali tagħhom jew li l-għadd għoli tal-plejtlets tagħhom ma jitnaqqasx għal-livell aċċettabbli bit-terapija attwali tagħhom.

Pazjent li jkun f'riskju
Pazjent bi trombożitemija essenzjali li jkun f'riskju huwa ddefinit b'waħda jew aktar mill-karatteristiċi li ġejjin:
- `il fuq minn 60 sena jew
- għadd tal-plejtlets > 1000 x 10^9/l jew
- passat mediku ta' reazzjonijiet trombo-emorraġiċi.

4.2 Pożoloġija u metodu ta' kif għandu jingħata

Trattament b'Xagrid għandu jinbeda minn tabib b'esperjenza fl-immaniġġjar ta' trombożitemija essenzjali.

Id-doża tal-bidu rrakkomandata ta' anagrelide huwa ta' 1 mg/jum, li għandu jingħata oralment f'żewġ dożi maqsumin (0.5 mg/doża).

Id-doża tal-bidu għandha tinżamm għal tal anqas ġimgħa. Wara ġimgħa d-doża għandha tiġi mibdula fuq bażi individwali, biex tinkiseb l-anqas doża effettiva meħtieġa biex tnaqqas u/jew iżżomm l-għadd tal-plejtlets anqas minn 600 x 10^9/l u idejalment f'livelli bejn 150 x 10^9/l u 400 x 10^9/l. Iż-żieda fid-doża m'għandhiex tkun aktar minn 0.5 mg/jum fi kwalunkwe ġimgħa u d-doża waħdanija massima rakkomandata m'għandhiex taqbeż 2.5 mg (ara sezzjoni 4.9). Waqt żvilupp kliniku ntużaw dożi ta' 10 mg/jum.

L-effetti ta' trattament b'anagrelide għandhom jiġu mmonitorjati fuq bażi reġolari (ara sezzjoni 4.4). Jekk id-doża tal-bidu hija > 1 mg/jum, l-għadd tal-plejtlets għandu jsir kull jumejn matul l-ewwel

ġimgħa tat-trattament u tal-anqas kull ġimgħa minn hemm ’l quddiem sakemm tintlaħaq doża stabbli li tinżamm. Tipikament, tnaqqis fl-għadd tal-plejtlets għandu jiġi osservat fi żmien 14 sa 21 ġurnata minn mindu jinbeda t-trattament u fil-parti l-kbira tal-pazjenti reazzjoni terapewtika adegwata tiġi osservata u miżmuma f’doża ta’ 1 sa 3 mg/jum (għal aktar informazzjoni fuq l-effetti kliniċi ara sezzjoni 5.1).

Anzjani
Id-differenzi farmakokinetiċi osservati bejn pazjenti anzjani u żgħażagħ bl-ET (ara sezzjoni 5.2) ma jiġġustifikawx l-użu ta’ kors tal-bidu differenti jew pass differenti tat-titrazzjoni tad-doża biex jittwettaq kors ta’ anagrelide li jkun ottimizzat għall-pazjent individwali.

Waqt l-iżvilupp kliniku bejn wieħed u ieħor 50% tal-pazjenti ttrattati b’anagrelide kellhom età ’l fuq minn 60 sena u l-ebda tibdil speċifiku fid-doża minħabba l-età ma kien meħtieġ f’dawn il-pazjenti. Madankollu, kif mistenni, pazjenti f’dan il-grupp ta’ età kellhom inċidenza doppja ta’ reazzjonijiet avversi (prinċipalment kardijaċi).

Indeboliment renali
Hemm dejta farmakokinetika limitata għal din il-popolazzjoni ta’ pazjenti. Ir-riskju potenzjali u s-siwi ta’ terapija b’anagrelide f’pazjent b’indeboliment tal-funzjoni renali għandhom jiġu valutati qabel ma jinbeda t-trattament.

Indeboliment epatiku
Hemm dejta farmakokinetika limitata għal din il-popolazzjoni ta’ pazjenti. Madankollu, il-metaboliżmu epatiku jirrappreżenta l-passaġġ ewlieni ta’ eliminazzjoni tal-mediċina u l-funzjoni tal-fwied għalhekk tista’ tiġi mistennija li tinfluwenza dan il-proċess. Għalhekk huwa rrakkomandat li pazjenti b’indeboliment moderat jew serju ma jiġux ittrattati b’anagrelide.Ir-riskji potenzjali u s-siwi ta’ terapija b’anagrelide f’pazjent b’indeboliment ħafif tal-funzjoni epatika għandhom jiġu mkejla qabel ma jinbeda t-trattament (ara sezzjonijiet 4.3 u 4.4).

Popolazzjoni pedjatrika
L-esperjenza fit-tfal hi limitata; anagrelide għandu jintuża bl-attenzjoni f’dan il-grupp ta’ pazjenti. Dejta disponibbli hi deskritta fis-sezzjonijiet 5.1 u 5.2, iżda l-ebda rakkomandazzjoni dwar il-pożoloġija ma tista’ tingħata.

4.3 Kontra-indikazzjonijiet

Sensittività eċċessiva għal anagrelide jew għal xi kwalunkwe wieħed mill-eċċipjenti.
Pazjenti b'indeboliment epatiku moderat jew serju.
Pazjenti b'indeboliment renali moderat jew serju (rata ta' eliminazzjoni tal-krejatinina < 50 ml/min).

4.4 Twissijiet speċjali u prekawzjonijiet għall-użu

Indeboliment epatiku
Ir-riskji potenzjali u s-siwi ta’ terapija b’anagrelide f’pazjent b’indeboliment ħafif tal-funzjoni epatika għandhom jiġu valutati qabel ma jinbeda t-trattament. Mhux rrakkomandat f’pazjenti bi transaminases għoljin (> 5 darbiet mil-limitu ta’ fuq tan-normal) (ara sezzjonijiet 4.2 u 4.3).

Indeboliment renali
Ir-riskji potenzjali u s-siwi ta’ terapija b’anagrelide f’pazjenti b’indeboliment ħafif tal-funzjoni renali għandhom jiġu valutati qabel ma jinbeda t-trattament (ara sezzjonijiet 4.2 u 4.3).

Monitoraġġ
It-terapija li għandha tinkludi l-għadd tad-demm komplut (emoġlobina u ċelloli bojod tad-demm u għadd tal-plejtlets), u stima ta’ testijiet tal-funzjoni tal-fwied (ALT u AST) u tal-funzjoni renali (krejatinina fis-serum u ureja) teħtieġ sorveljanza klinika mill-qrib tal-pazjent.

Plejtlets
L-għadd tal-plejtlets jiżdied fi żmien 4 ijiem mit-twaqqif ta' trattament bil- kapsuli ta' Xagrid u jirritorna għal-livelli ta' qabel it-trattament fi żmien 10 sa 14-il jum.

Kardjovaskulari
Avvenimenti avversi kardjovaskulari serji li jinkludu każijiet ta' kardjomijopatija, kardjomegalija, insuffiċjenza konġestiva tal-qalb u arritmiji kardijaċi ġew irrappurtati (ara sezzjoni 4.8).

Anagrelide għandu jintuża b'kawtela f'pazjenti ta' kull età b'mard tal-qalb magħruf jew issuspettat. Flimkien ma' dan, avvenimenti avversi kardjovaskulari serji seħħew ukoll f'pazjenti mingħajr mard tal-qalb issuspettat u b'eżami kardjovaskulari normali qabel il-kura.

Anagrelide għandu jintuża biss jekk il-benefiċċji potenzjali tat-terapija jegħlbu r-riskji potenzjali.

Anagrelide hu impeditur ta' AMP phosphodiesterase III ċikliku u minħabba l-effetti inotropiċi pożittivi tiegħu, eżami kardjovaskulari qabel il-kura (li jinkludi investigazzjoni addizzjonali bħal ekokardjografija, elettrokardjogramma) hu rakkomandat. Waqt il-kura, il-pazjenti għandhom jiġu mmonitorjati għal evidenza ta' effetti kardjovaskulari li jistgħu jeħtieġu iktar eżamijiet u investigazzjonijiet.

Popolazzjoni pedjatrika
Hemm dejta limitata dwar l-użu ta' anagrelide fil-popolazzjoni pedjatrika u anagrelide għandu jintuża b'kawtela f'dan il-grupp ta' pazjenti (ara sezzjonijiet 5.1 u 5.2).

Interazzjonijiet klinikament rilevanti
Anagrelide huwa impeditur ta' AMP phosphodiesterase III ċikliku (PDE III). L-użu ta' anagrelide flimkien ma' impedituri oħrajn PDE III bħal ma huma milrinone, amrinone, enoximone, olprinone u cilostazol mhux rakkomandat.

Eċċipjenti
Xagrid fih lactose. Pazjenti bi problemi rari ereditarji ta' intolleranza għal galactose, defiċjenza tal-lactase ta' Lapp jew assorbiment ħażin ta' glucose-galactose, m'għandhomx jieħdu dan il-prodott mediċinali.

4.5 Interazzjoni ma' prodotti mediċinali oħra u forom oħra ta' interazzjoni

Saru għadd limitat ta' studji farmakokinetiċi u/jew farmakodinamiċi li jistħarrġu r-reazzjonijiet possibbli bejn anagrelide u prodotti mediċinali oħrajn.

Interazzjonijiet mediċinali: effetti ta' sustanzi oħrajn fuq anagrelide:
- Anagrelide huwa metabolizzat primarjament minn CYP1A2. Huwa magħruf li CYP1A2 huwa impedut minn diversi prodotti mediċinali, li jinkludu fluvoxamine u omeprazole, u prodotti mediċinali bħal dawn jistgħu teoritikament jinfluwenzaw b'mod ħażin ir-rata ta' l-eliminazzjoni ta' anagrelide.
- Studji ta' interazzjonijet *in vivo* fil-bnedmin urew li digoxin u warfarin ma jaffetwawx il-kwalitajiet farmakokinetiċi ta' anagrelide.

Interazzjonijiet mediċinali: effetti ta' anagrelide fuq sustanzi oħrajn:
- Anagrelide juri xi attività inibitorja limitata lejn CYP1A2 li tista' tippreżenta potenzjal teoretiku għal interazzjonijiet ma' prodotti mediċinali oħrajn mogħtija flimkien li għandhom l-istess mekkaniżmu ta' eliminazzjoni eż. theophylline.
- Anagrelide huwa impeditur ta' PDE III. L-effetti ta' prodotti mediċinali bi kwalitajiet simili bħall-inotropi milrinone, enoximone, amrinone, olprinone u cilostazol jistgħu jiħraxu permezz ta' anagrelide.
- Studji ta' interazzjonijiet *in vivo* fil-bnedmin urew li anagrelide ma jaffettwax il-kwalitajiet farmakokinetiċi ta' digoxin jew warfarin.

- Fid-doži rakkomandati għal użu fit-trattament ta’ trombocitemja essenzjali, anagrelide jista’ jqawwi l-effetti ta’ prodotti mediċinali oħra li jimpedixxu jew jimmodifikaw il-funzjoni tal-plejtlets eż.acetylsalicylic acid.
- Studju dwar interazzjoni klinika li sar fuq persuni b’saħħithom wera li l-għoti flimkien ta’ doża ripetuta ta’ anagrelide 1 mg darba kuljum u acetylsalicylic acid 75 mg darba kuljum jista’ jtejjeb l-effetti tal-aggregazzjoni tal-anti-plejtlits ta’ kull mediċina meta mqabbel mal-għoti ta’ acetylsalicylic acid waħdu. F’xi pazjenti b’ET li ngħataw kura fl-istess ħin b’acetylsalicylic acid u anagrelide, seħħew emorraġiji maġġuri. Għalhekk, ir-riskji potenzjali tal-użu fl-istess ħin ta’ anagrelide ma’ acetylsalicylic acid għandhom jiġu evalwati, partikularment f’pazjenti bi profil ta’ riskju għoli għal emorraġija qabel tinbeda l-kura.
- Anagrelide jista’ jikkaġuna disturbi intestinali f’ xi pazjenti u jikkompromettu l-assorbiment ta’ kontraċettivi ormonali orali.

Interazzjonijiet ma’ l-ikel
- L-ikel idewwem l-assorbiment ta’ anagrelide imma ma jbiddilx b’mod sinifikanti l-espożizzjoni sistemika.
- L-effetti ta’ l-ikel fuq il-bijodisponibiltà mhumiex ikkunsidrati li huma klinikament rilevanti għall-użu ta’ angrelide.

Popolazzjoni pedjatrika
Studji ta’ interazzjoni twettqu biss f’adulti.

4.6 Fertilità, tqala u treddigħ

Nisa f’età li jista’ jkollhom it-tfal
Nisa li jistgħu joħorġu tqal għandhom jużaw kontraċettiv effettiv waqt it-trattament b’anagrelide.

Tqala
M'hemmx dejta biżżejjed dwar l-użu ta' anagrelide f'nisa tqal. Studji fl-annimali urew effett tossiku fuq is-sistema riproduttiva (ara sezzjoni 5.3). Ir-riskju li jista' jkun hemm għall-bniedem m'huwiex magħruf. L-użu ta' Xagrid mhux irrikkmandat waqt it-tqala.

Jekk Xagrid jintuża waqt it-tqala, jew jekk il-pazjenta toħroġ tqila waqt li tkun qed tuża l-prodott mediċinali, għandha tiġi avżata dwar ir-riskju potenzjali għall-fetu.

Treddigħ
Mhux magħruf jekk anagrelide hydrochloride/metaboliti jiġux eliminati mill-ħalib tas-sider. Ir-riskju għat-tarbija tat-twelid/tfal żgħar mhux eskluż. It-treddigħ għandu jitwaqqaf waqt it-trattament b’Xagrid.

Fertilità
M’hemmx dejta disponibbli dwar il-fertilità fuq anagrelide.

4.7 Effetti fuq il-ħila biex issuq u tħaddem magni

Ma sarux studji dwar l-effetti fuq il-ħila biex issuq u t-tħaddim ta’ magni.

Fl-iżvilupp kliniku, l-isturdament kien irrappurtat ta’ sikwit. Il-pazjenti għandhom jiġu avżati biex ma jsuqux jew iħaddmu inġenji meta jkunu qed jieħdu Xagrid jekk ikollhom isturdament.

4.8 Effetti mhux mixtieqa

Is-sigurtà ta' anagrelide ġiet eżaminata f'4 studji kliniċi *open label*. Fi 3 mill-istudji 942 pazjent li rċevew anagrelide f'doża medja ta' madwar 2 mg/jum ġew assessjati għas-sigurà. F'dawn l-istudji 22 pazjent irċevew anagrelide sa 4 snin.

Fi studju li sar aktar tard 3660 pazjent li rċevew anagrelide f'doża medja ta' madwar 2 mg/jum ġew assessjati għas-sigurtà. F'dan l-istudju 34 pazjent irċevew anagrelide sa 5 snin.

L-aktar reazzjoni avversa komuni relatat mal-mediċina rrapportata kienet l-uġigħ ta' ras li seħħet f'madwar 14%, palpitazzjonijiet li seħħew, f'madwar 9%, akkumulazzjoni ta' fluwidu u nawsja li t-tnejn seħħew f'madwar 6%, u dijarea li seħħet f'5%. Dawn ir-reazzjonijiet avversi tal-mediċina huma mistennija skond il-farmakoloġija ta' anagrelide (inpediment ta' PDE III). Titrazzjoni gradwali tad-doża tista' tgħin biex tnaqqas dawn l-effetti (ara sezzjoni 4.2).

Sommarju tabulat ta' reazzjonijiet avversi
Reazzjonijiet avversi li jirriżultaw mill-studji kliniċi, studji dwar is-sigurtà wara l-awtorizzazzjoni, u rapporti spontanji huma ppreżentati fit-tabella hawn taħt. Fil-klassijiet tas-sistema tal-organi, qed jintiżżlu taħt it-titli li ġejjin: Komuni ħafna (≥ 1/10); Komuni (≥ 1/100 sa < 1/10); Mhux komuni (≥ 1/1,000 sa < 1/100); Rari (≥ 1/10,000 sa < 1/1,000); Rari ħafna (< 1/10,000), mhux magħrufa (ma tistax tittieħed stima mid-data disponibbli).

Klassi tas-Sistema tal-Organi MedDRA	Frekwenza ta' Reazzjonijiet Avversi				
	Komuni ħafna	*Komuni*	*Mhux komuni*	*Rari*	*Mhux magħrufa*
Disturbi tad-demm u tas-sistema limfatika		Anemija	Trombożitopenija Panċitopenija Ekkimożi Emorraġija		
Disturbi fil-metaboliżmu u n-nutrizzjoni		Żamma ta' fluwidu	Edema Telf ta' piż	Żieda fil-piż	
Disturbi fis-sistema nervuża	Uġigħ ta' ras	Sturdament	Parestesija Nuqqas ta' rqad Dipressjoni Konfużjoni Ipoestesija Nervożiżmu Ħalq niexef Amnesija	Ngħas Koordinazzjoni anormali Disartrija Emigranja	
Disturbi fl-għajnejn				Vista anormali Diplopja	
Disturbi fil-widnejn u fis-sistema labirintika				Żanżin fil-widnejn	
Disturbi fil-qalb		Palpitazzjonijiet Takikardija	Insuffiċjenza konġestiva tal-qalb Pressjoni għolja Arritmija Fibrillazzjoni atrijali Takikardja supraventrikulari Takikardija ventrikulari Sinkope	Angina pectoris Infart mijokardijali Kardjomegalija Kardjomijopatija Effużjoni mill-perikardju Vażodilatazzjoni Pressjoni baxxa li tiddependi mill-qagħda	

Klassi tas-Sistema tal-Organi MedDRA	Frekwenza ta' Reazzjonijiet Avversi				
	Komuni ħafna	*Komuni*	*Mhux komuni*	*Rari*	*Mhux magħrufa*
Disturbi respiratorji, toraċiċi u medjastinali			Dispneja Tinfaraġ Effużjoni mill-plewra Pnewmonja	Pressjoni tad-demm pulmonari għolja Infiltrati pulmonari	Alveolite allerġika, li tinkludi mard interstizjali tal-pulmun u pnewmonite
Disturbi gastro-intestinali		Nawseja Dijarea Uġigħ addominali Gass Rimettar	Dispepsja Anoreksja Pankreatite Stitikezza Emorraġija gastrointestinali Disturb gastrointestinali	Kolite Gastrite Ħruġ ta' demm ġinġivali	
Disturbi fil-fwied u fil-marrara			Żieda fl-enzimi tal-fwied		Epatite
Disturbi fil-ġilda u fit-tessuti ta' taħt il-ġilda		Raxx	Alopeċja Tibdil fil-kulur tal-ġilda Ħakk	Ġilda xotta	
Disturbi muskolu-skeletriċi u tat-tessuti konnettivi			Mijalġja Artralġja Uġigħ fid-dahar		
Disturbi fil-kliewi u fis-sistema urinarja			Impotenza	Nokturja Insuffiċjenza tal-kliewi	Nefrite tubule-interstizjali
Disturbi ġenerali u kondizzjonijiet ta' mnejn jingħata:		Għeja kbira	Uġigħ fis-sider Dgħjufija Tertir ta' bard Telqa Deni	Astenja Uġigħ Sindrome qisu influwenza	
Investigazzjoniji et				Żieda fil-krejatinina tad-demm	

4.9 Doża eċċessiva

Ġew irċevuti rapporti ta' wara t-tqegħid fis-suq dwar dożaġġ eċċessiv intenzjonali b'anagrelide. Sintomi rrapportati jinkludu sinus, takikardja u rimettar. Is-sintomi ġew riżolti b'manigment konservattiv.

Xagrid, f'doži ogħla minn dawk rakkomandati, intwera li jipproduċi tnaqqis fil-pressjoni tad-demm b'xi każijiet okkażjonali ta' pressjoni baxxa tad-demm. Doża waħda ta' 5 mg ta' anagrelide tista' twassal għal tnaqqis fil-pressjoni tad-demm normalment akkompanjata minn sturdament.

Ma ġie identifikat l-ebda antidot għal anagrelide. F'każ ta' doża eċċessiva, sorveljanza klinika mill-qrib hija meħtieġa; din tinkludi monitoraġġ ta' l-għadd tal-plejtlets għat-trombożitopenja. Id-doża għandha titnaqqas jew titwaqqaf, kif suppost, sakemm l-għadd tal-plejtlets jerġa' jiġi fil-livelli normali.

5. PROPRJETAJIET FARMAKOLOĠIĊI

5.1 Proprjetajiet farmakodinamiċi

Kategorija farmakoterapewtika: Sustanzi antineoplastiċi oħrajn, Kodiċi ATC: L01XX35.

Il-mekkaniżmu ta' azzjoni speċifika li bih anagrelide jnaqqas l-għadd tal-plejtlets s'issa mhux mifhum kompletament għalkemm ġie konfermat minn informazzjoni ta' studji *in vitro* u *in vivo* li anagrelide huwa selettiv għal plejtlets.

Studji *in vitro* ta' megakarjoċitopoeżi umana stabbilixxew li l-azzjonijiet inibitorji ta' anagrelide fuq il-formazzjoni tal-plejtlets fil-bniedem huma medjati permezz ta' dewmien fil-maturazzjoni tal-megakarjoċiti, u bi tnaqqis tad-daqs u l-ploidy tagħhom. Evidenza ta' azzjonijiet simili *in vivo* kienet osservata f'kampjuni tal-bijopsiji mill-mudullun ta' pazjenti trattati.

Anagrelide huwa impeditur ta' cyclic AMP phosphodiesterase III.

Is-sigurtà u l-effikaċja ta' anagrelide bħala mediċina li tbaxxi l-għadd tal-plejtlets kienu evalwati f'erba' provi kliniċi open-label u mhux ikkontrollati (in-numri ta' l-istudji 700-012, 700-014, 700-999 u 13970-301) li nkludew aktar minn 4000 pazjent b'disturbi majeloproliferattivi (MPDs). F'pazjenti b'trombożitemja essenzjali, respons komplut kien definit bħala tnaqqis fl-għadd tal-plejtlets għal $\leq 600 \times 10^9$/l jew tnaqqis ta' ≥ 50% mil-linja bażi ta' riferimet u tat-tnaqqis jibqa' għal ta' l-anqas 4 ġimgħat. Il-ħin biex jintlaħaq respons komplut fl-istudji 700-012, 700-014, 700-999 u l-istudju 13970-301varja minn 4 sa 12-il ġimgħa. Ma ġiex muri b'konvinzjoni s-siwi kliniku f'termini ta' reazzjonijiet tromboemorraġiċi.
Popolazzjoni pedjatrika
Studju kliniku, open label b'perijodu ta' trattament ta' 3 xhur ma qajjimx tħassib dwar is-sigurtà ta' anagrelide fi 17-il tifel jew tifla/adolexxenti b'ET (età ta' bejn is-7 u l-14-il sena) meta mqabbel ma' 18-il pazjent adult. Aktar kmieni fi żvilupp kliniku għadd limitat (12) ta' tfal (età ta' bejn il-5 u s-17-il sena) bi trombożitemja essenzjali kienu ttrattati b'anagrelide.

Dan il-prodott mediċinali kien awtorizzat taħt 'ċirkustanzi eċċezzjonali' Dan ifisser li minħabba li l-marda hija rari, ma kienx possibbli li tinkiseb informazzjoni kompluta dwar il-prodott mediċinali. L-Aġenzija Ewropea għall-Mediċini ser tirrevedi kull tip ta' informazzjoni ġdida li toħroġ kull sena u ser taġġorna dan is-Sommarju tal-Karatteristiċi tal-Prodott, skont il-bżonn.

5.2 Tagħrif farmakokinetiku

Wara l-għoti orali ta' anagrelide fil-bniedem, ta' l-anqas 70% jiġi assorbit mill-passaġġ gastrointestinali. F'individwi sajmin, il-livelli massimi fil-plażma jseħħu f'madwar siegħa wara doża ta' 0.5 mg; il-*half-life* fil-plażma hija qasira, madwar 1.3 sigħat. Il-proporzjonalità fid-doża nstabet f'doża li tvarja minn 0.5 mg sa 2 mg.

Anagrelide huwa primarjament metabolizzat minn CYP1A2; anqas minn 1% huwa rikoverat fl-awrina bħala anagrelide. Żewġ metaboliti maġġuri fl-awrina, 2-amino-5, 6-dichloro-3, 4-dihydroquinazoline u 3-hydroxy anagrelide ġew identifikati. L-irkupru medju ta' 2-amino-5, 6-dichloro-3, 4-dihydroquinazoline fl-awrina huwa ta' bejn wieħed u ieħor 18%-35% tad-doża mogħtija.

Dejta farmakokinetika minn individwi f'saħħithom stabbilixxiet li l-ikel inaqqas is-C_{max} ta' anagrelide b'14% imma jżid l-AUC b' 20%. L-ikel kellu effett aktar sinifikattiv fuq il-metabolit attiv u naqqas is-C_{max} b' 29% għalkemm ma kellu l-ebda effett fuq l-AUC.

Kif mistenni mill-half-life tiegħu, m'hemm l-ebda evidenza ta' akkumulazzjoni ta' anagrelide fil-plażma. Barra minn hekk dawn ir-riżultati ma juru l-ebda evidenza ta' awto-induzzjoni ta' l-eliminazzjoni ta' anagrelide.

Popolazzjoni pedjatrika
Dejta farmakokinetika minn tfal u adolexxenti sajmin (età ta' bejn is 7 u l-14-il sena) b'trombocitemja essenzjali indikat li esponimenti nnormalizzati tad-doża u tal-piż korporali, is-C_{max} u l-AUC ta' anagrelide kienu aktar baxxi fit-tfal/adolexxenti meta mqabbla ma' ta' l-adulti. Kien hemm ukoll tendenza li jitbaxxa l-esponiment għal metabolit attiv. Dawn l-osservazzjonijiet jistgħu jkunu riflessjoni ta' eliminazzjoni metabolika aktar effiċjenti f'individwi iżgħar.

Anzjani
Dejta farmakokinetika minn pazjenti anzjani fl-istat sajjem b'ET (età ta' bejn il-65 u l-75 sena) meta mqabbla ma' pazjenti adulti fl-istat sajjem (età ta' bejn it-22 u l-50 sena) tindika li s-C_{max} u l-AUC ta' anagrelide kienu 36% u 61% ogħla rispettivament f'pazjenti anzjani, iżda li s-C_{max} u l-AUC tal-metabolit attiv, 3-hydroxy anagrelide, kienu 42% u 37% iktar baxxi fil-pazjenti anzjani. Dawn id-differenzi kienu x'aktarx ikkawżati minn metaboliżmu presistemiku iktar baxx ta' anagrelide għal 3-hydroxy anagrelide fil-pazjenti anzjani.

5.3 Tagħrif ta' qabel l-użu kliniku dwar is-sigurtà

Fi studji li mhumiex kliniċi, l-effetti dehru biss wara esponimenti meqjusa ferm aktar għolja mill-massimu ta' esponiment fil-bniedem, li juru ftit li xejn rilevanza għall-użu kliniku.

Tossiċità ta' doži rrepetuti
Wara l-għoti ripetut ta' anagrelide, f'doži ta' 1 mg/kg/jum jew ogħla, kien hemm emorraġija sottoendokardjali u nekroži mijokardjali fokali fil-klieb.
Tossiċità fis-sistema riproduttiva
Doži ta' anagrelide li huma tossiċi fil-maternita' (60 mg/kg/jum jew aktar) fil-firien u fil-fniek kienu assoċjati ma żieda fir-risorbiment ta' l-embriju u tal-mortalità tal-fetu.

Potenzjal mutaġeniku u karċinoġeniku
Studji fuq il-potenzjal ġenotossiku ta' anagrelide ma identifika l-ebda effett mutaġeniku jew klastoġeniku.

Fi studju dwar il-karċinoġeneċità fil-firien li dam sentejn, kienu osservati sejbiet non-neoplastiċi u neoplastiċi, li kienu marbuta jew attribwiti ma' effett farmakoloġiku esaġerat. Fosthom, l-inċidenza ta' phaeochromocytomas adrenali żdiedet meta mqabbla mal-kontroll fil-firien maskili fil-livelli kollha tad-doża (≥ 3 mg/kg/kuljum) u fil-firien femminili li kienu qed jirċievu 10 mg/kg/kuljum u aktar. L-inqas doża f'dawk maskili (3 mg/kg/kuljum) tikkorrispondi għal 37 darba ta' l-espożizzjoni ta' l-AUC fil-bniedem wara doża ta' 1 mg darbtejn kuljum. Adenokarċinomi fl-utru, ta' oriġini epiġenetika, jistgħu jkunu marbuta ma' induzzjoni ta' enżima tal-familja CYP1. Dawn kienu osservati fil-firien femminili li kienu qed jirċievu 30 mg/kg/kuljum, li jikkorrispondu għal 572 darba ta' l-espożizzjoni ta' l-AUC fil-bniedem wara doża ta' 1 mg darbtejn kuljum.

6. TAGĦRIF FARMAĊEWTIKU

6.1 Lista ta' eċċipjenti

X'fihom il-kapsuli
Povidone (E1201)
Anhydrous lactose

Lactose monohydrate
Microcrystalline cellulose (E460)
Crospovidone
Magnesium stearate

Il-qoxra tal-kapsula
Gelatin
Titanium dioxide (E171)

Linka ta' l-istampar
Shellac
Soluzzjoni qawwija ta' ammonium
Potassium hydroxide (E525)
Black iron oxide (E172)

6.2 Inkompatibbilitajiet

Mhux applikabbli

6.3 Żmien kemm idum tajjeb il-prodott mediċinali

4 snin

6.4 Prekawzjonijiet speċjali għall-ħażna

Din il-mediċina m'għandhiex bżonn ħażna speċjali. **6.5 In-natura tal-kontenitur u ta' dak li hemm ġo fih**

Fliexken ta' *high-density polyethylene* (HDPE) b'għatu li ma jinfetaħx mit-tfal u dessikant li fihom 100 kapsula.

6.6 Prekawzjonijiet speċjali li għandhom jittieħdu meta jintrema

L-ebda ħtiġijiet speċjali.

7. ID-DETENTUR TAL-AWTORIZZAZZJONI GĦAT-TQEGĦID FIS-SUQ

Shire Pharmaceutical Contracts Ltd
Hampshire International Business Park
Chineham
Basingstoke
Hampshire RG24 8EP
Ir-Renju Unit

8. NUMRU(I) TAL-AWTORIZZAZZJONI GĦAT-TQEGĦID FIS-SUQ

EU/1/04/295/001

9. DATA TAL-EWWEL AWTORIZZAZZJONI/TIĠDID TAL-AWTORIZZAZZJONI

Data tal-ewwel awtorizzazzjoni: 16/11/2004
Data tal-aħħar tiġdid: 16/11/2009

10. DATA TA' REVIŻJONI TAT-TEST

01/2013

Informazzjoni dettaljata dwar dan il-prodott mediċinali tinsab fuq is-sit elettroniku tal-Aġenzija Ewropea għall-Mediċini http://www.ema.europa.eu.

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CONFIDENTIAL

23 January 2013

Ref: EU/1/04/295/001 – S/048 – MT (EN)

Direct Healthcare ProfessionalCommunication

on the association of anagrelide hydrochloride (Xagrid® 0.5mg hard capsules) with cardiovascular risk in patients with essential thrombocythaemia (ET)

Dear Healthcare Professional,

Communication on the association of anagrelide hydrochloride (Xagrid® 0.5mg hard capsules) with cardiovascular risk in patients with essential thrombocythaemia (ET), whatever the patient's medical history or medical condition, and a reminder that the indication for anagrelide is second line therapy in at risk essential thrombocythaemia patients.

Summary

Following a review of all cardiac events reported in patients under 50 years of age treated with anagrelide, section 4.4 'Special warnings and precautions for use', cardiovascular section of the Xagrid Summary of Product Characteristics (SmPC) has been re-enforced.

A statement has been added stating that serious cardiovascular adverse events may occur in patients without any suspected heart disease and with normal previous cardiovascular investigations.

The addition of this statement to the Xagrid SmPC does not alter the current benefit/risk of anagrelide in the context of its therapeutic indication as a second line treatment in at risk essential thrombocythaemia (ET) patients.

The communication of this information has been agreed with the European Medicines Agency and the Medicines Authority.

Further information on the safety concern

Recently, as part of ongoing surveillance, Shire conducted a review of all cardiac events reported in patients under 50 years of age treated with anagrelide. Serious cardiovascular adverse events have occurred in these younger patients with no suspected heart disease, normal cardiovascular pre-treatment examinations and controlled myeloproliferative disease.

This led to re-enforcing the cardiovascular warning in Section 4.4 ‘Special precautions and warnings for use’ of the EU SmPC.

Also in the same section of the EU SmPC, the list of serious cardiovascular adverse reactions has been expanded to include cardiomyopathy and cardiac arrhythmias, to be consistent with the tabulated summary of adverse events (Section 4.8). Changes are shown in red and are underlined below.

> **Special warnings and precautions for use**
>
> *Cardiovascular*
>
> Serious cardiovascular adverse events including cases of cardiomyopathy, cardiomegaly, congestive heart failure and cardiac arrhythmias have been reported (see section 4.8).
>
> Anagrelide should be used with caution in patients of any age with known or suspected heart disease. Moreover, serious cardiovascular adverse events have also occurred in patients without suspected heart disease and with normal pre-treatment cardiovascular examination.
>
> Anagrelide should only be used if the potential benefits of therapy outweigh the potential risks.
>
> Anagrelide is an inhibitor of cyclic AMP phosphodiesterase III and because of its positive inotropic effects, a pre-treatment cardiovascular examination (including further investigation such as echocardiography, electrocardiogram) is recommended. Patients should be monitored during treatment for evidence of cardiovascular effects that may require further cardiovascular examination and investigation.

Further information on recommendations to healthcare professionals

Healthcare Professionals are reminded that patients should be monitored before and during treatment for evidence of cardiovascular effects that may require further cardiovascular examination and investigation. This is in order to detect any possible cardiovascular effects and in order for appropriate care to be given to patients.

Xagrid is indicated for the reduction of elevated platelet counts in at risk essential thrombocythaemia (ET) patients who are intolerant to their current therapy or whose elevated platelet counts are not reduced to an acceptable level by their current therapy. An at risk essential thrombocythaemia patient is defined by one or more of the following features:

- >60 years of age or
- a platelet count > 1000 x 10^9/l or
- a history of thrombo-haemorrhagic events.

Call for reporting

Please report any adverse events experienced by your patients taking anagrelide. When reporting, please provide as much information as possible including information about medical history, any concomitant medication, onset and treatment dates.

Suspected adverse drug reaction should be reported to the Malta Medicines Authority at: Medicines Authority Post-licensing Directorate, 203, Level 3, Rue D'Argens, Gzira GZR 1368, MALTA, or by use of http://www.medicinesauthority.gov.mt/pub/adr.doc.

Adverse events should also be reported to Shire:

Via e-mail to: GlobalPharmacovigilance@shire.com

Tel number: +44 1256 894000

Fax number: +44 1256 894715

Should you have any questions, please contact the Shire Medical Information Department represented by Vivian Corporation Ltd.:

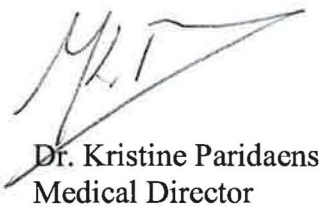
Tel: +356 – 21320338/21344610/21344616. Email: pv@viviancorp.com

Marketing Authorisation Holder

Shire Pharmaceutical Contracts Limited
Hampshire International Business Park
Chineham, Basingstoke
Hampshire
RG24 8EP
United Kingdom.

Yours faithfully,

Dr. Birgitt Gellert
Vice President Medical Surveillance and
European Qualified Person for Pharmacovigilance



Dr. Kristine Paridaens
Medical Director

Enclosures

Text of the revised SmPC(s) with changes highlighted

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Xagrid 0.5 mg hard capsules.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 0.5 mg anagrelide (as anagrelide hydrochloride).

Excipients
Each hard capsule contains lactose monohydrate (53.7 mg) and anhydrous lactose (65.8 mg).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

An opaque white hard capsule imprinted with S 063.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Xagrid is indicated for the reduction of elevated platelet counts in at risk essential thrombocythaemia (ET) patients who are intolerant to their current therapy or whose elevated platelet counts are not reduced to an acceptable level by their current therapy.

An at risk patient
An at risk essential thrombocythaemia patient is defined by one or more of the following features:

- > 60 years of age or
- a platelet count > 1000 x 10^9/l or
- a history of thrombo-haemorrhagic events.

4.2 Posology and method of administration

Treatment with Xagrid should be initiated by a clinician with experience in the management of essential thrombocythaemia.

The recommended starting dose of anagrelide is 1 mg/day, which should be administered orally in two divided doses (0.5 mg/dose).

The starting dose should be maintained for at least one week. After one week the dose may be titrated, on an individual basis, to achieve the lowest effective dose required to reduce and/or maintain a platelet count below 600 x 10^9/l and ideally at levels between 150 x 10^9/l and 400 x 10^9/l. The dose increment must not exceed more than 0.5 mg/day in any one-week and the recommended maximum single dose should not exceed 2.5 mg (see section 4.9). During clinical development doses of 10 mg/day have been used.

The effects of treatment with anagrelide must be monitored on a regular basis (see section 4.4). If the starting dose is > 1 mg/day platelet counts should be performed every two days during the first week of treatment and at least weekly thereafter until a stable maintenance dose is reached. Typically, a fall

in the platelet count will be observed within 14 to 21 days of starting treatment and in most patients an adequate therapeutic response will be observed and maintained at a dose of 1 to 3 mg/day (for further information on the clinical effects refer to section 5.1).

Elderly
The observed pharmacokinetic differences between elderly and young patients with ET (see section 5.2) do not warrant using a different starting regimen or different dose titration step to achieve an individual patient-optimised anagrelide regimen.

During clinical development approximately 50% of the patients treated with anagrelide were over 60 years of age and no age specific alterations in dose were required in these patients. However, as expected, patients in this age group had twice the incidence of serious adverse events (mainly cardiac).

Renal impairment
There are limited pharmacokinetic data for this patient population. The potential risks and benefits of anagrelide therapy in a patient with impairment of renal function should be assessed before treatment is commenced.

Hepatic impairment
There are limited pharmacokinetic data for this patient population. However, hepatic metabolism represents the major route of drug clearance and liver function may therefore be expected to influence this process. Therefore it is recommended that patients with moderate or severe hepatic impairment are not treated with anagrelide. The potential risks and benefits of anagrelide therapy in a patient with mild impairment of hepatic function should be assessed before treatment is commenced (see sections 4.3 and 4.4).

Paediatric population
The experience in children is limited; anagrelide should be used in this patient group with caution. Currently available data are described in sections 5.1 and 5.2 but no recommendation on a posology can be made.

4.3 Contraindications

Hypersensitivity to anagrelide or to any of the excipients.
Patients with moderate or severe hepatic impairment.
Patients with moderate or severe renal impairment (creatinine clearance < 50 ml/min).

4.4 Special warnings and precautions for use

Hepatic impairment
The potential risks and benefits of anagrelide therapy in a patient with mild impairment of hepatic function should be assessed before treatment is commenced. It is not recommended in patients with elevated transaminases (> 5 times the upper limit of normal) (see sections 4.2 and 4.3).

Renal impairment
The potential risks and benefits of anagrelide therapy in a patient with impairment of renal function should be assessed before treatment is commenced (see sections 4.2 and 4.3).

Monitoring
Therapy requires close clinical supervision of the patient which will include a full blood count (haemoglobin and white blood cell and platelet counts), and assessment of liver function (ALT and AST) and renal function (serum creatinine and urea) tests.

Platelets
The platelet count will increase within 4 days of stopping treatment with Xagrid capsules and will return to pre-treatment levels within 10 to 14 days.

Cardiovascular
Serious cardiovascular adverse events including cases of cardiomyopathy, cardiomegaly, congestive heart failure and cardiac arrhythmias have been reported (see section 4.8).

Anagrelide should be used with caution in patients of any age with known or suspected heart disease. Moreover, serious cardiovascular adverse events have also occurred in patients without suspected heart disease and with normal pre-treatment cardiovascular examination.

Anagrelide should only be used if the potential benefits of therapy outweigh the potential risks.

Anagrelide is an inhibitor of cyclic AMP phosphodiesterase III and because of its positive inotropic effects, a pre-treatment cardiovascular examination (including further investigation such as echocardiography, electrocardiogram) is recommended. Patients should be monitored during treatment for evidence of cardiovascular effects that may require further cardiovascular examination and investigation.

Paediatric population
Limited data are available on the use of anagrelide in the paediatric population and anagrelide should be used in this patient group with caution (see sections 5.1 and 5.2).

Clinically relevant interactions
Anagrelide is an inhibitor of cyclic AMP phosphodiesterase III (PDE III). Concomitant use of anagrelide with other PDE III inhibitors such as milrinone, amrinone, enoximone, olprinone and cilostazol is not recommended.

Excipients
Xagrid contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Limited pharmacokinetic and/or pharmacodynamic studies investigating possible interactions between anagrelide and other medicinal products have been conducted.

Drug interactions: effects of other substances on anagrelide
- Anagrelide is primarily metabolised by CYP1A2. It is known that CYP1A2 is inhibited by several medicinal products, including fluvoxamine and omeprazole, and such medicinal products could theoretically adversely influence the clearance of anagrelide.
- *In vivo* interaction studies in humans have demonstrated that digoxin and warfarin do not affect the pharmacokinetic properties of anagrelide.

Drug interactions: effects of anagrelide on other substances
- Anagrelide demonstrates some limited inhibitory activity towards CYP1A2 which may present a theoretical potential for interaction with other co-administered medicinal products sharing that clearance mechanism e.g. theophylline.
- Anagrelide is an inhibitor of PDE III. The effects of medicinal products with similar properties such as the inotropes milrinone, enoximone, amrinone, olprinone and cilostazol may be exacerbated by anagrelide.
- *In vivo* interaction studies in humans have demonstrated that anagrelide does not affect the pharmacokinetic properties of digoxin or warfarin.
- At the doses recommended for use in the treatment of essential thrombocythaemia, anagrelide may potentiate the effects of other medicinal products that inhibit or modify platelet function e.g. acetylsalicylic acid.
- A clinical interaction study performed in healthy subjects showed that co-administration of repeat-dose anagrelide 1 mg once daily and acetylsalicylic acid 75 mg once daily may enhance the anti-platelet aggregation effects of each drug compared with administration of acetylsalicylic acid alone. In some ET patients concomitantly treated by acetylsalicylic acid and anagrelide,

- Anagrelide may cause intestinal disturbance in some patients and compromise the absorption of hormonal oral contraceptives.

Food interactions
- Food delays the absorption of anagrelide, but does not significantly alter systemic exposure.
- The effects of food on bioavailability are not considered clinically relevant to the use of anagrelide.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential
Women of child-bearing potential should use adequate birth-control measures during treatment with anagrelide.

Pregnancy
There are no adequate data from the use of anagrelide in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Therefore Xagrid is not recommended during pregnancy.

If Xagrid is used during pregnancy, or if the patient becomes pregnant while using the medicinal product, she should be advised of the potential risk to the foetus.

Breast-feeding
It is unknown whether anagrelide hydrochloride/metabolites are excreted in milk. A risk to the newborn/infant cannot be excluded. Breast-feeding should be discontinued during treatment with Xagrid.

Fertility
There are no fertility data available on anagrelide.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

In clinical development, dizziness was commonly reported. Patients are advised not to drive or operate machinery while taking Xagrid if dizziness is experienced.

4.8 Undesirable effects

The safety of anagrelide has been examined in 4 open label clinical studies. In 3 of the studies 942 patients who received anagrelide at a mean dose of approximately 2 mg/day were assessed for safety. In these studies 22 patients received anagrelide for up to 4 years.

In the later study 3660 patients who received anagrelide at a mean dose of approximately 2 mg/day were assessed for safety. In this study 34 patients received anagrelide for up to 5 years.

The most commonly reported drug related adverse reactions were headache occurring at approximately 14%, palpitations occurring at approximately 9%, fluid retention and nausea both occurring at approximately 6%, and diarrhoea occurring at 5%. These adverse drug reactions are expected based on the pharmacology of anagrelide (inhibition of PDE III). Gradual dose titration may help diminish these effects (see section 4.2).

Tabulated summary of adverse reactions

Adverse reactions arising from clinical studies, post-authorisation safety studies and spontaneous reports are presented in the table below. Within the system organ classes they are listed under the following headings: Very common (≥ 1/10); Common (≥ 1/100 to < 1/10); Uncommon (≥ 1/1,000 to < 1/100); Rare (≥ 1/10,000 to < 1/1,000); Very rare (< 1/10,000), not known (cannot be estimated from the available data).

MedDRA System Organ Class	Frequency of Adverse Reactions				
	Very common	*Common*	*Uncommon*	*Rare*	*Not known*
Blood and lymphatic system disorders		Anaemia	Thrombocytopenia Pancytopenia Ecchymosis Haemorrhage		
Metabolism and nutrition disorders		Fluid retention	Oedema Weight loss	Weight gain	
Nervous system disorders	Headache	Dizziness	Paraesthesia Insomnia Depression Confusion Hypoaesthesia Nervousness Dry mouth Amnesia	Somnolence Abnormal coordination Dysarthria Migraine	
Eye disorders				Vision abnormal Diplopia	
Ear and labyrinth disorders				Tinnitus	
Cardiac disorders		Palpitations Tachycardia	Congestive heart failure Hypertension Arrhythmia Atrial fibrillation Supraventricular tachycardia Ventricular tachycardia Syncope	Angina pectoris Myocardial infarction Cardiomegaly Cardiomyopathy Pericardial effusion Vasodilatation Postural hypotension	
Respiratory, thoracic and mediastinal disorders			Dyspnoea Epistaxis Pleural effusion Pneumonia	Pulmonary hypertension Pulmonary infiltrates	Allergic alveolitis, including interstitial lung disease and pneumonitis
Gastrointestinal disorders		Nausea Diarrhoea Abdominal pain Flatulence Vomiting	Dyspepsia Anorexia Pancreatitis Constipation Gastrointestinal haemorrhage Gastrointestinal disorder	Colitis Gastritis Gingival bleeding	

MedDRA System Organ Class	Frequency of Adverse Reactions				
	Very common	*Common*	*Uncommon*	*Rare*	*Not known*
Hepatobiliary disorders			Hepatic enzymes increased		Hepatitis
Skin and subcutaneous tissue disorders		Rash	Alopecia Skin discoloration Pruritus	Dry skin	
Musculoskeletal and connective tissue disorders			Myalgia Arthralgia Back pain		
Renal and urinary disorders			Impotence	Nocturia Renal failure	Tubulointerstitial nephritis
General disorders and administration site conditions		Fatigue	Chest pain Weakness Chills Malaise Fever	Asthenia Pain Flu-like syndrome	
Investigations				Blood creatinine increased	

4.9 Overdose

Post-marketing case reports of intentional overdose with anagrelide have been received. Reported symptoms include sinus tachycardia and vomiting. Symptoms resolved with conservative management.

Xagrid, at higher than recommended doses, has been shown to produce reductions in blood pressure with occasional instances of hypotension. A single 5 mg dose of anagrelide can lead to a fall in blood pressure usually accompanied by dizziness.

A specific antidote for anagrelide has not been identified. In case of overdose, close clinical supervision of the patient is required; this includes monitoring of the platelet count for thrombocytopenia. Dose should be decreased or stopped, as appropriate, until the platelet count returns to within the normal range.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antineoplastic agents, ATC Code: L01XX35

The specific mechanism of action by which anagrelide reduces platelet count is not yet fully understood although it has been confirmed that anagrelide is platelet selective from *in vitro* and *in vivo* study information.

In vitro studies of human megakaryocytopoiesis established that anagrelide's inhibitory actions on platelet formation in man are mediated via retardation of maturation of megakaryocytes, and reducing

their size and ploidy. Evidence of similar *in vivo* actions was observed in bone marrow biopsy samples from treated patients.

Anagrelide is an inhibitor of cyclic AMP phosphodiesterase III.

The safety and efficacy of anagrelide as a platelet lowering agent have been evaluated in four open-label, non-controlled clinical trials (study numbers 700-012, 700-014, 700-999 and 13970-301) including more than 4000 patients with myeloproliferative disorders (MPDs). In patients with essential thrombocythaemia complete response was defined as a decrease in platelet count to $\leq 600 \times 10^9$/l or a $\geq 50\%$ reduction from baseline and maintenance of the reduction for at least 4 weeks. In studies 700-012, 700-014, 700-999 and study 13970-301 the time to complete response ranged from 4 to 12 weeks. Clinical benefit in terms of thrombohaemorrhagic events has not been convincingly demonstrated.

Paediatric population
An open label clinical study with a 3 month treatment period did not raise any safety concerns for anagrelide in 17 children/adolescent patients with ET (age range 7 - 14 years) compared to 18 adult patients. Earlier during clinical development a limited number (12) of children (age range 5 - 17 years) with essential thrombocythaemia were treated with anagrelide.

This medicinal product has been authorised under "Exceptional Circumstances".
This means that due to the rarity of this disease it has not been possible to obtain complete information on this medicine.
The European Medicines Agency will review any new information which may become available every year and this SPC will be updated as necessary.

5.2 Pharmacokinetic properties

Following oral administration of anagrelide in man, at least 70% is absorbed from the gastrointestinal tract. In fasted subjects, peak plasma levels occur about 1 hour after a 0.5 mg dose; the plasma half-life is short, approximately 1.3 hours. Dose proportionality has been found in the dose range 0.5 mg to 2 mg.

Anagrelide is primarily metabolised by CYP1A2; less than 1% is recovered in the urine as anagrelide. Two major urinary metabolites, 2-amino-5, 6-dichloro-3, 4-dihydroquinazoline and 3-hydroxy anagrelide have been identified. The mean recovery of 2-amino-5, 6-dichloro-3, 4-dihydroquinazoline in urine is approximately 18-35% of the administered dose.

Pharmacokinetic data from healthy subjects established that food decreases the C_{max} of anagrelide by 14%, but increases the AUC by 20%. Food had a more significant effect on the active metabolite and decreased the C_{max} by 29%, although it had no effect on the AUC.

As expected from its half-life, there is no evidence for anagrelide accumulation in the plasma. Additionally these results show no evidence of auto-induction of the anagrelide clearance.

Paediatric population
Pharmacokinetic data from fasting children and adolescents (age range 7 - 14 years) with essential thrombocythaemia indicate that dose and body weight normalised exposure, C_{max} and AUC, of anagrelide were lower in children/adolescents compared to adults. There was also a trend to lower exposure to the active metabolite. These observations may be a reflection of more efficient metabolic clearance in younger subjects.

Elderly
Pharmacokinetic data from fasting elderly patients with ET (age range 65 - 75 years) compared to fasting adult patients (age range 22 - 50 years) indicate that the C_{max} and AUC of anagrelide were 36% and 61% higher respectively in elderly patients, but that the C_{max} and AUC of the active metabolite, 3-hydroxy anagrelide, were 42% and 37% lower respectively in the elderly patients. These differences

were likely to be caused by lower presystemic metabolism of anagrelide to 3-hydroxy anagrelide in the elderly patients.

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Repeated dose toxicity
Following repeated administration of anagrelide, at doses of 1 mg/kg/day or higher, subendocardial haemorrhage and focal myocardial necrosis occurred in dogs.

Reproductive toxicology
Maternally toxic doses of anagrelide (60 mg/kg/day and above) in rats and rabbits were associated with increased embryo resorption and foetal mortality.

Mutagenic and carcinogenic potential
Studies on the genotoxic potential of anagrelide did not identify any mutagenic or clastogenic effects.

In a two-year rat carcinogenicity study, non-neoplastic and neoplastic findings were observed and related or attributed to an exaggerated pharmacological effect. Among them, the incidence of adrenal phaeochromocytomas was increased relative to control in males at all dose levels (≥ 3 mg/kg/day) and in females receiving 10 mg/kg/day and above. The lowest dose in males (3 mg/kg/day) corresponds to 37 times the human AUC exposure after a 1 mg twice daily dose. Uterine adenocarcinomas, of epigenetic origin, could be related to an enzyme induction of CYP1 family. They were observed in females receiving 30 mg/kg/day, corresponding to 572 times the human AUC exposure after a 1 mg twice daily dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents
Povidone (E1201)
Anhydrous lactose
Lactose monohydrate
Microcrystalline cellulose (E460)
Crospovidone
Magnesium stearate

Capsule shell
Gelatin
Titanium dioxide (E171)

Printing ink
Shellac
Strong ammonium solution
Potassium hydroxide (E525)
Black iron oxide (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

4 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

High-density polyethylene (HDPE) bottles with child-resistant closures and desiccant containing 100 capsules.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Shire Pharmaceutical Contracts Ltd
Hampshire International Business Park
Chineham
Basingstoke
Hampshire RG24 8EP
United Kingdom

8. MARKETING AUTHORISATION NUMBER

EU/1/04/295/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16/11/2004
Date of latest renewal: 16/11/2009

10. DATE OF REVISION OF THE TEXT

01/2013

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu