

에피엔트® 정

5 / 10 밀리그램
(프라수그렐염산염)



【원료약품 및 그 분량】

5밀리그램 - 1정(31.25밀리그램)중-

주성분 : 프라수그렐 염산염 5.49밀리그램
(프라수그렐로서 5밀리그램)

10밀리그램 -1정(181.25밀리그램)중-

주성분 : 프라수그렐 염산염 10.98밀리그램
(프라수그렐로서 10밀리그램)

【성상】

5밀리그램 : 황색의 육각형 모양 필름 코팅 정제

10밀리그램 : 미황색의 육각형 모양 필름 코팅 정제

【효능 · 효과】

관상동맥중재술(percutaneous coronary intervention PCI)이 예정된 다음의 급성관상동맥중후군 환자에서 스텐트 혈전증을 포함한 혈전성 심혈관 사건(심혈관 질환으로 인한 사망, 치명적이지 않은 심근경색 또는 치명적이지 않은 뇌졸중)의 발생을 감소
- 불안정형 협심증(UA) 또는 비- ST 분절 상승 심근경색(NSTEMI) 환자
- 일차적 또는 지연 관상동맥중재술(primary or delayed PCI)을 받은 ST 분절 상승 심근경색(STEMI) 환자

【용법 및 용량】

- 1) 성인
이 약은 체중이 60 킬로그램 이상이고 연령이 75세 미만(체중 $\geq$ 60 kg, 연령 < 75세)인 성인에 한하여, 부하용량으로 프라수그렐로서 60밀리그램을 단회 경구투여한 후, 유지용량으로 1일 1회 10밀리그램을 투여한다. 다만, 출혈경향성이 높은 환자인 경우 유지용량으로 1일 1회 5밀리그램을 투여한다. (사용상의 주의사항 중 1, 경고 및 3, 다음 환자에는 신중히 투여할 것, 중 출혈 위험 요인 참조)
식사와 관계없이 이 약을 투여하며, 아스피린(1일 75 ~ 325 밀리그램)과 병용투여하여야 한다.
- 2) 신장에 환자
신장에 환자에 대한 용량 조절은 필요하지 않으나, 이 약의 사용 경험이 제한적이므로 신중하게 투여하여야 한다.
- 3) 간장에 환자
경증 내지 중증도의 간장애(Child Pugh Class A 및 B) 환자에 대한 용량 조절은 필요하지 않으나, 이 약의 사용 경험이 제한적이므로 신중하게 투여하여야 한다.
- 4) 소아 및 청소년
18세 이하의 소아 및 청소년 환자에 대한 안전성·유효성이 확립되어 있지 않다.

【사용상의 주의사항】

1. 경고
이 약은 유의하고, 때때로 치명적인 출혈을 유발할 수 있다.(4. 이상반응 참조) 병리학적 활동성 출혈이 있는 환자나 일과성 허혈 발작 혹은 뇌졸중에 대한 병력이 있는 환자에게 이 약을 투여해서는 안 된다. (2. 다음 환자에는 신중히 투여할 것, 중 출혈 위험 요인 참조)
75세 이상(연령 $\geq$ 75세)의 고령자는 치명적인 출혈 및 두개내 출혈 위험성 증가, 불확실한 유익성으로 인하여 이 약의 투여가 권장되지 않는다.
또한 체중이 60 킬로그램 미만(체중 < 60 kg)인 경우 출혈 위험성 증가로 인하여 이 약의 투여가 권장되지 않는다.
관상동맥우회술(coronary-artery bypass graft, CABG)을 받을 가능성이 있는 환자인 경우 이 약의 투여를 시작하지 않으며, 가능한 한 모든 수술 전 적어도 7일 전에 이 약의 투여를 중단한다.
출혈에 대한 추가 위험 요인은 다음과 같다.
- 출혈 경향성
- 출혈의 위험을 증가시킬 수 있는 약물(예 : 와파린, 헤파린, 클로피도그렐, 비스테로이드성 소염제(NSAIDs), 혈전용해제, 당단백 IIb/ IIIa 저해제 등)의 병용투여
최근에 관상동맥중재술, 경피적 관상동맥중재술(PCI), 관상동맥우회술(CABG), 기타 외과적 수술을 받은 환자로서, 이 약 투여시 저혈압 증상이 나타나면 출혈을 의심해야 한다.
가능하면 이 약의 투여를 중단하지 않고 출혈을 치료하도록 한다. 특히 급성 관상동맥중후군 발생 후 수주 이내 이 약의 투여 중단시, 심혈관 사건에 대한 위험이 증가한다.(5. 일반적 주의 참조)

2. 다음 환자에는 투여하지 말 것

- 1) 이 약의 구성성분에 과민증이 있는 환자
- 2) 소화성 궤양 또는 두개내 출혈과 같은 병리학적 활동성 출혈이 있는 환자
- 3) 뇌졸중 또는 일과성 허혈 발작(TIA)에 대한 병력이 있는 환자
- 4) 중증의 간장애 환자(Child Pugh class C)
- 5) 이 약은 유당을 함유하고 있으므로, 갈락토오스 불내성(galactose intolerance), Lapp 유당분해효소 결핍증(Lapp lactase deficiency) 또는 포도당-갈락토오스 흡수장애(glucose-galactose malabsorption) 등의 유전적인 문제가 있는 환자에게는 투여하면 안 된다.

3. 다음 환자에는 신중히 투여할 것

- 1) 출혈 위험성
이 약을 포함한 티에노피리딘계 약물은 출혈에 대한 위험성을 증가시킨다. 3상 임상시험(TRITON-TIMI 38)에서 출혈 위험성 증가, 빈혈, 혈소판 감소증, 두개내 병리소견에 대한 병력이 주요 제외기준에 포함되었음에도 불구하고, 관상동맥중재술(PCI)을 받은 급성 관상동맥중후군 환자에게 이 약과 아스피린을 병용투여한 결과, TIMI (Thrombolysis in Myocardial Infarction) 분류 기준에 따른 대 출혈(major bleeding) 및 소출혈(minor bleeding)의 위험성이 증가하였다. 따라서, 출혈 위험성이 높은 환자인 경우 허혈 사건의 예방과 관련된 이익이 심각한 출혈의 위험성을 상회한다고 판단되는 경우에만 이 약의 투여가 고려되어야 한다.
출혈에 대한 추가 위험요인은 다음과 같다.
- 75세 이상의 연령 (치명적인 출혈 및 두개내 출혈에 대한 위험성 증가, 불확실한 유익성으로 인하여 이 약의 투여가 권장되지 않는다.)
- 관상동맥중재술(CABG) 또는 다른 수술 과정
- 출혈 경향성(예: 최근의 외상, 최근의 수술, 최근 또는 재발성 위장관 출혈, 활동성 소화성 궤양 등)
- 60 킬로그램 미만의 체중 (출혈 위험성 증가로 인하여 이 약의 투여가 권장되지 않는다.)
- 출혈의 위험을 증가시킬 수 있는 약물의 투여 (예 : 와파린, 헤파린, 클로피도그렐, 비스테로이드성 소염제(NSAIDs), 혈전용해제, 당단백 IIb/ IIIa 저해제 등)
최근에 관상동맥중재술, 경피적 관상동맥중재술(PCI), 관상동맥우회술(CABG), 기타 외과적 수술을 받은 환자로서, 이 약 투여시 저혈압 증상이 나타나면 출혈을 의심해야 한다.
- 2) 관상동맥우회술(CABG) 관련 출혈
관상동맥우회술을 받은 환자에서 이 약 투여시 출혈 위험성이 증가하므로 이 수술을 받을 가능성이 있는 환자인 경우 이 약의 투여를 시작하지 않으며, 가능한 한 수술 전 적어도 7일 전에 이 약의 투여를 중단한다.
- 3) 신장에 환자 및 간장애 환자
이 약의 치료 경험은 제한적이다. 이러한 환자들은 출혈 위험성이 증가될 수 있으므로, 이 약 투여시 주의하여야 한다.
- 4) 혈전성 혈소판 감소성 자색반증 (Thrombotic Thrombocytopenic Purpura, TTP)
혈전성 혈소판 감소성 자색반증은 다른 티에노피리딘계 투여 후 드물게 보고되었으며, 때때로 단기간 투여(2주 이내) 후에도 보고되었다. 이러한 질환은 중대한 증상으로 치명적일 수 있으며, 혈장교환술(혈장교환법)과 같은 즉각적인 치료가 요구된다. 혈전성 혈소판 감소성 자색반증은 혈소판감소증, 미소혈관 용혈성 빈혈(분절적혈구절단된 적혈구)가 미세도말표본에서 관찰, 신경학적 소견, 신부전 및 발열을 특징적으로 나타낸다. 이 약으로 실시된 임상시험에서는 혈전성 혈소판 감소성 자색반증이 보고되지 않았다.
- 5) 아시아인
코카시안이 주로 참여한 3상 임상시험에서 체중이 60 킬로그램 이상인 환자군 보다 60 킬로그램 미만인 환자군에서 프라수그렐 활성대사체의 AUC가 약 30 ~ 40% 증가하였으며 출혈 발생률이 더 높게 보고되어, 체중이 60 킬로그램 미만인 환자에 대해 유지용량으로 프라수그렐 5밀리그램 투여가 권장되었다.
아시아인 환자에 대한 이 약의 치료 경험은 제한적이다. 이 약의 유지용량인 프라수그렐 10밀리그램에 대한 약동학 메타분석 결과, 프라수그렐 활성대사체에 대한 아시아인(중국인, 일본인, 한국인)의 AUC가 코카시안에 비해 약 40% 증가하였으며, 약학적 평가변수인 혈소판응집제 저항도 더 높았다. 이에 대해 체중을 고려한 하위분석 결과, 체중 60 킬로그램 이상인 건강한 아시아인의 AUC가 코카시안에 비해 약간 증가하였으며(약 19%), 체중이 60 킬로그램 미만인 경우 AUC가 더 많이 증가하였다(약 45%), 또한 체중과 연령을 함께 고려한 하위분석 결과, 체중이 60 킬로그램 이상이며 75세 미만(체중 $\geq$ 60 kg, 연령 < 75세)인 건강한 아시아인의 AUC가 코카시안에 비해 약 22% 증가하였다. 이러한 프라수그렐 활성대사체의 체내 노출(AUC) 증가는 출혈 위험성을 증가시킬 수 있으므로, 신중한 용량 결정 및 출혈에 대한 주의깊은 모니터링이 요구된다.

4. 이상반응

- 이 약의 안전성은 경피적 관상동맥중재술(PCI)이 예정된 급성관상동맥중후군 환자 6741명을 대상으로 14.5개월(중양값)의 기간 동안 이 약(프라수그렐)을 투여한 3상 임상시험(TRITON-TIMI 38)에서 평가되었다. 이 약은 부하용량으로 60mg 단회 경구투여 후 유지용량으로 1일 1회 10밀리그램 투여하였으며, 대조군으로 클로피도그렐(부하용량으로 300밀리그램 단회 경구투여 후 유지용량으로 1일 1회 75밀리그램을 투여하였다. 이 시험에 참여한 모든 피험자에게 아스피린을 함께 투여하였으며, 이 중 5802 명은 6개월 이상 투여하였고, 4136명은 1년 이상 투여하였다.
- 이상반응으로 인한 임상시험 중단율은 프라수그렐 투여군에서 7.2%, 클로피도그렐 투여군에서 6.3%였다. 시험약의 중단이 요구되었던 가장 흔한 이상반응은 두 약물 모두 출혈이었다(프라수그렐 투여군 2.5%, 클로피도그렐 투여군 1.4%).
- 출혈**
1) 비-CABG 관련 출혈
3상 임상시험에서 관상동맥우회술(CABG)과 관련이 없는 출혈의 발생율은 표1과 같다. 불안정형 협심증/비-ST 분절 상승 심근경색 및 전체 급성관상동맥중후군 환자에서 생명을 위협하는 출혈 및 치명적인 출혈을 포함한 비-CABG 관련 TIMI 대출혈 또는 소출혈의 발생율은 클로피도그렐 투여군에 비해 이 약 투여군에서 통계적으로 유의하게 더 높았으며, ST분절 상승 심근경색 환자군에서는 투여군간 유의한 차이가 없었다. 가장 흔한 출혈 부위는 위장관 출혈이었다(프라수그렐 투여군 1.7%, 클로피도그렐 투여군 1.3%), 가장 많이 보고된 출혈 부위는 동맥 전자 부위였다(프라수그렐 투여군 1.3%, 클로피도그렐 투여군 1.2%).
- [표1.] 비-CABG 관련 출혈의 발생율 a (환자의 %).

발생율	전체 관상동맥중후군		불안정형 협심증/ 비ST 분절 상승 심근경색		ST-분절 상승 심근경색	
	프라수그렐 ^b +아스피린 (N=6741)	클로피도그렐 ^b +아스피린 (N=6716)	프라수그렐 ^b +아스피린 (N=5001)	클로피도그렐 ^b +아스피린 (N=4980)	프라수그렐 ^b (N=1740)	클로피도그렐 ^b +아스피린 (N=1736)
TIMI 대출혈 ^c	2.2	1.7	2.2	1.6	2.2	2.0
- 생명을 위협하는 출혈 ^d	1.3	0.8	1.3	0.8	1.2	1.0
- 치명적	0.3	0.1	0.3	0.1	0.4	0.1
- 증상성 두개내 출혈 (ICH) ^e	0.3	0.3	0.3	0.3	0.2	0.2
- 수술중지장애가 요구	0.3	0.1	0.3	0.1	0.3	0.2
- 수술적 중재가 요구	0.3	0.3	0.3	0.3	0.1	0.2
- 수혈 요구($\geq$ 4 units)	0.7	0.5	0.6	0.3	0.8	0.8
TIMI 소출혈 ^f	2.4	1.9	2.3	1.6	2.7	2.6

- a TIMI 분류기준에서 정한 정의에 따라 판정하였다.
b 기타 표준 요법은 적절하게 사용하였다.
c 모든 두개내 출혈 또는 헤모글로빈이 5g/dL 이상 감소와 관련된 임상적으로 명백한 출혈을 의미한다.
d 생명을 위협하는 출혈은 TIMI 대출혈의 하위 분류로, 환자들은 중복 평가될 수 있다.
e ICH : intracranial haemorrhage. (두개내 출혈)
f 3g/dL < 헤모글로빈 < 5g/dL의 감소와 관련된 임상적으로 명백한 출혈을 의미한다.
- 2) 체중과 연령을 고려한 출혈
3상 임상시험에서 연령 및 체중에 따른 비-CABG-관련 TIMI 대출혈 또는 소출혈 발생율은 표2와 같다:
[표2.] 체중과 연령에 따른 비-CABG 관련 출혈 발생율 (%)
- | 구분 | | 프라수그렐 + 아스피린 | 클로피도그렐 + 아스피린 |
|-------------------------------|---------------------|---------------------|---------------|
| 연령 $\geq$ 75 세 (N = 1785) | 9.0% (치명적인 출혈 1.0%) | 6.9% (치명적인 출혈 0.1%) | |
| 연령 < 75 세 (N = 11672) | 3.8% (치명적인 출혈 0.2%) | 2.9% (치명적인 출혈 0.1%) | |
| 체중 < 60 킬로그램 (N = 664) | 10.1% (치명적인 출혈 0%) | 6.5% (치명적인 출혈 0.3%) | |
| 체중 $\geq$ 60 킬로그램 (N = 12672) | 4.2% (치명적인 출혈 0.3%) | 3.3% (치명적인 출혈 0.1%) | |
- 체중이 60 킬로그램 이상이고 75세 미만인 환자에서, 비-CABG 관련 TIMI 대출혈 또는 소출혈의 발생율은 프라수그렐 투여군에서 3.6%, 클로피도그렐 투여군에서 2.8%였으며, 치명적인 출혈의 발생율은 프라수그렐 투여군에서 0.2%, 클로피도그렐 투여군에서 0.1%였다.
- 3) CABG-관련 출혈
3상 임상시험에서, 437명의 환자들이 임상시험 도중에 관상동맥우회술(CABG)을 받았다. 관상동맥우회술과 관련된 TIMI 대출혈 또는 소출혈의 발생율은 프라수그렐 투여군에서 14.1%, 클로피도그렐 투여군에서 4.5%였다. 프라수그렐을 투여한 환자에서 출혈 위험성이 더 높은 것은 시험약의 마지막 투여일로부터 최대 7일간 지속되었다.
[표3.] CABG-관련 출혈 발생율 (%)

발생율	프라수그렐 + 아스피린 (N = 213)	클로피도그렐 + 아스피린 (N = 224)	발생율	프라수그렐 + 아스피린 (N = 213)	클로피도그렐 + 아스피린 (N = 224)
TIMI 대출혈	11.3 %	3.6 %	- 수혈 요구($\geq$ 5 units)	6.6 %	2.2 %
- 치명적	0.9 %	0 %	- 두개내 출혈 (ICH)	0 %	0 %
- 재수술	3.8 %	0.5 %	TIMI 소출혈	2.8 %	0.9 %

관상동맥우회술 전 3일 이내에 이 약 또는 대조약을 투여한 환자에서, TIMI 대출혈 또는 소출혈의 발생율은 프라스그렐 투여군에서 26.7% (45명 중 12명)인 반면, 클로피도그렐 투여군에서 5.0%(60명 중 3명)이었다. 관상동맥우회술 전 4일 내지 7일 이내에 이 약 또는 대조약의 마지막 용량을 투여받은 환자에서 이 약의 발생율은 프라스그렐 투여군에서 11.3% (60명 중 9명), 클로피도그렐 투여군에서 3.4% (89명 중 3명)이다. 투약 중단 후 7일 경까지 관상동맥우회술 관련 출혈의 발생율이 투여군 간에 유사하였다.

	프라수그렐 + 아스피린	클로피도그렐 + 아스피린		프라수그렐 + 아스피린	클로피도그렐 + 아스피린
코피	6.2%	3.3%	시술 후 출혈	0.5%	0.2%
위장관 출혈	1.5%	1.0%	후복막 출혈	0.3%	0.2%
개혈	0.6%	0.5%	망막 출혈	0.0%	0.01%
피하의 출혈	0.5%	0.2%			

3. 다른 이상반응
3차 입산시험에서 보고된 기타 중요한 비출혈성 이상반응은 다음과 같다.

	프라스구렐 + 아스피린	클로피도그렐 + 아스피린		프라스구렐 + 아스피린	클로피도그렐 + 아스피린
심각한 혈소판 감소증	0.06%	0.04%	알레르기 반응	0.3%	0.36%
빈혈	2.2%	2.0%	혈관부종	0.06%	0.04%
비정상적인 간기능	0.22%	0.27%			

프루그글	글로피노글	프루그글	글로피노글
+ 아스피린	+ 아스피린	+ 아스피린	+ 아스피린

혈색소(헤모글로빈) / 적혈구	7.0%	7.4%	염색제	2.9%	3.1%
구름	5.5%	5.3%	사맥	2.8%	2.4%
요통	5.0%	4.5%	백혈구 감소증($<4 \times 10^9$ WBC/L)	2.8%	3.5%
호흡곤란	4.9%	4.5%	발진	2.8%	2.4%
구역	4.6%	1.3%	발열	2.7%	2.25%
어지러움	4.1%	4.6%	말초혈관 부종	2.7%	3.0%
기침	3.9%	4.1%	사지 동증	2.6%	2.6%
저혈압	3.9%	3.8%	설사	2.3%	2.6%
피로	3.7%	4.8%			

IIA 또는 뇌졸중 병력	프라부그렐 + 아스피린	클로피도그렐 + 아스피린
예 (N = 518)	6.5% (2.3% ICH*)	1.2% (0% ICH*)

5. 일반적 주의

6. 상호작용

4) 아스피린: 아스피린(111 150mg 투여)과 병용 투여시 프라수그렐에 의한 혈소판 응집 억제에 유의한 영향을 주지 않았으나, 개개 약효 단독 투여시에 비해 출혈 시간이 연장되었다. 이 약은 아스피린과 병용 투여하여야 한다. 아스피린과의 약력학적 상호작용을 통해 출혈 위험성이 증가될 가능성이 있지만, 이 약과 아스피린과 병용 투여한 환자에서 유혈성 및 안전성이 입증되었다.

5) 헤파린: 비분획 헤파린(100 U/kg)을 단회 정맥 주입시 이 약의 혈소판 응집 저해에 대한 유의한 영향이 없었다. 이와 마찬가지로, 이 약은 헤파린에 의한 응고에 대한 영향을 주지 않았다. 그러나, 개개 약효 단독 투여시에 비해 출혈 시간이 연장되었다.

6) 와파린: 와파린(1일 15mg 투여)과 병용 투여시 출혈시간이 유의하게 연장되었다.

7) 스타틴: 아토르바스타틴(1일 80mg 투여)과 병용 투여시 이 약의 약력학 및 혈소판 응집 저해에 유의한 영향이 없었다.

8) 위 pH를 상승시키는 약물: 위 약과 라니티딘(H2 차단제) 또는 란소졸라졸(프로톤펌프억제제)을 병용 투여시 프라수그렐 활성대사체의 AUC와 Tmax는 영향이 없었으나, Cmax가 각각 14% 및 23% 정도 감소하였다. 그러나, 3상 임상시험에서 이 약은 프로토펙트억제제 또는 H2 차단제 병용 여부와 관계없이 투여되었다.

9) CYP3A 저해제: 케토코나졸(1일 400 mg 투여)은 CYP3A4와 CYP3A5에 대한 선택적이고 강력한 저해제로, 이 약에 의한 혈소판 응집 저해는 및 프라수그렐 활성대사체의 AUC 및 Tmax에 영향을 주지 않았으나, Cmax를 34% ~ 46% 감소시켰다. 따라서, 출혈 위험성, HIV 단백분해효소 저해제, 클라트리모마이신, 텔리트리모마이신, 페라피린, 밀티엔젠, 인티바린, 시프로플록사신 및 자몽 주스와 같은 CYP3A 저해제는 프라수그렐 활성대사체의 약동학에 유의한 영향을 미치지 않을 것으로 예상된다.

10) 시트크롬 P450의 유도제: 리튬피신 (1일 600mg)은 CYP3A 및 CYP2B6의 강력한 유도제이며, CYP2C9, CYP2C19, 및 CYP2C8의 유도제로 프라수그렐 활성대사체의 약동학 및 혈소판 응집 저해에 유의한 영향을 주지 않았다. 따라서, 리튬피신, 카르바마제핀과 같은 CYP3A 유도제 및 기타 시트크롬 P450의 유도제는 프라수그렐 활성대사체의 약동학에 유의한 영향을 미치지 않을 것으로 예상된다.

기타 약물에 대한 프라수그렐의 영향:

1) 다독임: 이 약은 다독성의 약동학에 임상적으로 유의한 영향을 미치지 않는다.

2) CYP2C9에 의해 대사되는 약물: 이 약은 와파린의 약동학에 영향을 미치지 않았으므로, CYP2C9를 저해하지 않았다. 그러나, 출혈 위험성을 증가시킬 가능성이 있으므로, 이 약과 와파린 병용투여시 주의하여야 한다.

3) CYP2B6에 의해 대사되는 약물: 이 약은 CYP2B6의 약한 저해제이다. 건강한 피험자에서, 이 약은 CYP2B6에 의한 부프로피온의 대사체인 히드록시부프로피온의 체내 노출을 23% 감소시켰다. 따라서 이 약과 CYP2B6에 의해서만 대사되며, 치료효과가 좋은 약물 (예: 사이클로스포파미드, 에페리딘 등)과 병용투여시 주의가 요구될 수 있다.

7. 임부 및 수유부에 대한 투여

8. 소아에 대한

9. 운전 및 기계 조작에 대한 영향

10.고령자에 대한 투

11.과량 투여시의 처치

12.보관 및 취급상의 주의사항

13.기타

【포장단위】 30정/카톤 **【저장방법】** 실온보관(25℃이하), 기밀용기 **【사용(유효)기간】** 외부포장의 사용기한 참조
【제조원】
 제조자(외부(전공)정위탁제조) : Eli Lilly Nederland B.V., Grootslag 1-5, NL-3991 RA Houten, 네덜란드
 제조자(내부(공)정위탁제조) :
 포장제와 전공정] Eli Lilly and Company, Lilly Technology Center, Indianapolis, Indiana 46221, 미국
 포장] Lilly S.A., Avda de la Industria 30, 28108 Alcobendas, Madrid, 스페인

* 본 약약품은 엄격한 품질관리를 필한 제품입니다. 구입시 사용(유효)기한이 경과되거나 변질, 또는 오손된 제품은 구입한 약국 등 약약품 판매 업소에 한하여 본사 또는 영업소를 통하여 교환하여 드립니다.

* 이 제품설명서 작성(개정일자) 이후 변경된 내용은 홈페이지(www.jilly.co.kr)의 제품정보 또는 제품문의처 전화로(02-3459-2600)통해 확인 하실 수 있습니다.

* 약약품 용어 설명 및 기타 자세한 약약품 정보는 "이지드럭(ezdrug.kfda.go.kr)의약품 정보" 참조

EFFIENT
5 mg and 10 mg film-coated tablets
prasugrel (as hydrochloride)

1. NAME OF THE MEDICINAL PRODUCT

Effient 5 mg film-coated tablets.
Effient 10 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Effient 5 mg
Each tablet contains 5 mg prasugrel (as hydrochloride).
Excipient: Each tablet contains 2.7 mg lactose.

Effient 10 mg
Each tablet contains 10 mg prasugrel (as hydrochloride).
Excipient: Each tablet contains 2.1 mg lactose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Effient 5 mg
Yellow and double-arrow-shaped tablets, debossed with "5 MG" on one side and "4760" on the other.

Effient 10 mg
Beige and double-arrow shaped tablets, debossed with "10 MG" on one side and "4759" on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Effient, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in patients with acute coronary syndrome (i.e. unstable angina, non-ST segment elevation myocardial infarction [UA/NSTEMI] or ST segment elevation myocardial infarction [STEMI]) undergoing primary or delayed percutaneous coronary intervention (PCI).

For further information please refer to section 5.1.

4.2 Posology and method of administration

Posology

Adults

Effient should be initiated with a single 60 mg loading dose and then continued at 10 mg once a day. Patients taking Effient should also take ASA daily (75 mg to 325 mg).

In patients with acute coronary syndrome (ACS) who are managed with PCI, premature discontinuation of any antiplatelet agent, including Effient, could result in an increased risk of thrombosis, myocardial infarction or death due to the patient's underlying disease. A treatment of up to 12 months is recommended unless the discontinuation of Effient is clinically indicated (see sections 4.4 and 5.1).

Patients ≥ 75 years old

The use of Effient in patients ≥ 75 years of age is generally not recommended. If, after a careful individual benefit/risk evaluation by the prescribing physician (see section 4.4), treatment is deemed necessary in the patients age group ≥ 75 years, then following a 60 mg loading dose a reduced maintenance dose of 5 mg should be prescribed. Patients ≥ 75 years of age have greater sensitivity to bleeding and higher exposure to the active metabolite of prasugrel (see sections 4.4, 4.8, 5.1 and 5.2). The evidence for the 5 mg dose is based only on pharmacodynamic/pharmacokinetic analyses and no clinical data currently exist on the safety of this dose in the patients age group ≥ 75 years.

Patients weighing <60 kg

Effient should be given as a single 60 mg loading dose and then continued at a 5 mg once daily dose. The 10 mg maintenance dose is not recommended. This is due to an increase in exposure to the active metabolite of prasugrel, and an increased risk of bleeding in patients with body weight <60 kg when given a 10 mg once daily dose compared with patients ≥60 kg. Efficacy and safety of the 5 mg dose have not been prospectively assessed (see sections 4.4, 4.8 and 5.2).

Renal impairment

No dose adjustment is necessary for patients with renal impairment, including patients with end stage renal disease (see section 5.2). There is limited therapeutic experience in patients with renal impairment (see section 4.4).

Hepatic impairment

No dose adjustment is necessary in subjects with mild to moderate hepatic impairment (Child Pugh class A and B) (see section 5.2). There is limited therapeutic experience in patients with mild and moderate hepatic dysfunction (see section 4.4).

Children and adolescents

Effient is not recommended for use in children below age 18 due to a lack of data on safety and efficacy.

Method of administration

For oral use, Effient may be administered with or without food. Administration of the 60 mg prasugrel loading dose in the fasted state may provide most rapid onset of action (see section 5.2). Do not crush or break the tablet.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.
Active pathological bleeding.
History of stroke or transient ischaemic attack (TIA).
Severe hepatic impairment (Child Pugh class C).

4.4 Special warnings and precautions for use

Bleeding risk

In the phase 3 clinical trial key exclusion criteria included an increased risk of bleeding: anaemia; thrombocytopaenia; a history of pathological intracranial findings. Patients with acute coronary syndromes undergoing PCI treated with Effient and ASA showed an increased risk of major and minor bleeding according to the TIMI classification system. Therefore, the use of Effient in patients at increased risk of bleeding should only be considered when the benefits in terms of prevention of ischaemic events are deemed to outweigh the risk of serious bleedings. This concern applies especially to patients:

- ≥75 years of age (see below).
- with a propensity to bleed (e.g. due to recent trauma, recent surgery, recent or recurrent gastrointestinal bleeding, or active peptic ulcer disease)
- with body weight <60 kg (see sections 4.2 and 4.8). In these patients the 10 mg maintenance dose is not recommended. A 5 mg maintenance dose should be used.
- with concomitant administration of medicinal products that may increase the risk of bleeding, including oral anticoagulants, clopidogrel, non-steroidal anti-inflammatory drugs (NSAIDs), and fibrinolytics.

For patients with active bleeding for whom reversal of the pharmacological effects of Effient is required, platelet transfusion may be appropriate.

The use of Effient in patients ≥75 years of age is generally not recommended and should only be undertaken with caution after a careful individual benefit/risk evaluation by the prescribing physician indicates that benefits in terms of prevention of ischaemic events outweigh the risk of serious bleedings. In the phase 3 clinical trial these patients were at greater risk of bleeding, including fatal bleeding, compared to patients <75 years of age. If prescribed, a lower maintenance dose of 5 mg should be used; the 10 mg maintenance dose is not recommended (see sections 4.2 and 4.8).

Therapeutic experience with prasugrel is limited in patients with renal impairment (including ESRD) and in patients with moderate hepatic impairment. These patients may have an increased bleeding risk. Therefore, prasugrel should be used with caution in these patients.

Therapeutic experience with prasugrel is limited in Asian patients. Therefore, prasugrel should be used with caution in these patients.

Patients should be told that it might take longer than usual to stop bleeding when they take prasugrel (in combination with ASA), and that they should report any unusual bleeding (site or duration) to their physician.

Surgery

Patients should be advised to inform physicians and dentists that they are taking prasugrel before any surgery is scheduled and before any new medicinal product is taken. If a patient is to undergo elective surgery, and an antiplatelet effect is not desired, Effient should be discontinued at least 7 days prior to surgery. Increased frequency (3-fold) and severity of bleeding may occur in patients undergoing CABG surgery within 7 days of discontinuation of prasugrel (see 4.8). The benefits and risks of prasugrel should be carefully considered in patients in whom the coronary anatomy has not been defined and urgent CABG is a possibility.

Thrombotic Thrombocytopenic Purpura (TTP)

TTP has been reported with the use of other thienopyridines. TTP is a serious condition and requires prompt treatment. Effient was not associated with TTP in clinical trials supporting registration.

Effects of other medicinal products on Effient:

Acetylsalicylic acid: Effient is to be administered concomitantly with acetylsalicylic acid (ASA). Although a pharmacodynamic interaction with ASA leading to an increased risk of bleeding is possible, the demonstration of the efficacy and safety of prasugrel comes from patients concomitantly treated with ASA.

Heparin: A single intravenous bolus dose of unfractionated heparin (100 U/kg) did not significantly alter the prasugrel-mediated inhibition of platelet aggregation. Likewise, prasugrel did not significantly alter the effect of heparin on measures of coagulation. Therefore, both medicinal products can be administered concomitantly. An increased risk of bleeding is possible when Effient is co-administered with heparin.

Statins: Atorvastatin (80 mg daily) did not alter the pharmacokinetics of prasugrel and its inhibition of platelet aggregation. Therefore, statins that are substrates of CYP3A are not anticipated to have an effect on the pharmacokinetics of prasugrel or its inhibition of platelet aggregation.

Medicinal products that elevate gastric pH: Daily co-administration of ranitidine (an H₂ blocker) or lansoprazole (a proton pump inhibitor) did not change the prasugrel active metabolite's AUC and T_{max} but decreased the C_{max} by 14% and 29%, respectively. In the phase 3 clinical trial, Effient was administered without regard to co-administration of a proton pump inhibitor or H2 blocker. Administration of the 60 mg prasugrel loading dose without concomitant use of proton pump inhibitors may provide most rapid onset of action.

Inhibitors of CYP3A: Ketoconazole (400 mg daily), a selective and potent inhibitor of CYP3A4 and CYP3A5, did not affect prasugrel-mediated inhibition of platelet aggregation or the prasugrel active metabolite's AUC and T_{max} but decreased the C_{max} by 34% to 46%. Therefore, CYP3A inhibitors such as azol antifungals, HIV protease inhibitors, clarithromycin, telithromycin, verapamil, diltiazem, indinavir, ciprofloxacin, and grapefruit juice are not anticipated to have a significant effect on the pharmacokinetics of the active metabolite.

Inducers of cytochromes P450: Rifampicin (600 mg daily), a potent inducer of CYP3A and CYP2B6, and an inducer of CYP2C9, CYP2C19, and CYP2C8, did not significantly change the pharmacokinetics of prasugrel. Therefore, known CYP3A inducers such as rifampicin, carbamazepine, and other inducers of cytochromes P450 are not anticipated to have significant effect on the pharmacokinetics of the active metabolite.

Effects of Effient on other medicinal products:

Digoxin: prasugrel has no clinically significant effect on the pharmacokinetics of digoxin.

Medicinal products metabolised by CYP2C9: prasugrel did not inhibit CYP2C9, as it did not affect the pharmacokinetics of S-warfarin. Because of the potential for increased risk of bleeding, warfarin and Effient should be co-administered with caution (see section 4.4).

Medicinal products metabolised by CYP2B6: prasugrel is a weak inhibitor of CYP2B6. In healthy subjects, prasugrel decreased exposure to hydroxybupropion, a CYP2B6-mediated metabolite of bupropion, by 23%. This effect is likely to be of clinical concern only when prasugrel is co-administered with medicinal products for which CYP2B6 is the only metabolic pathway and have a narrow therapeutic window (e.g. cyclophosphamide, efavirenz).

4.6 Pregnancy and lactation

No clinical study has been conducted in pregnant or lactating women.

Animal studies do not indicate direct harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). Because animal reproduction studies are not always predictive of a human response, Effient should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the foetus.

It is unknown whether prasugrel is excreted in human breast milk. Animal studies have shown excretion of prasugrel in breast milk. The use of prasugrel during breastfeeding is not recommended.

Prasugrel had no effect on fertility of male and female rats at oral doses up to an exposure 240 times the recommended daily human maintenance dose (based on mg/m²).

4.7 Effects on ability to drive and use machines

No studies on the effects on ability to drive and use machines have been performed. Prasugrel is expected to have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Safety in patients with acute coronary syndrome undergoing PCI was evaluated in one clopidogrel-controlled study (TRITON) in which 6741 patients were treated with prasugrel (60 mg loading dose and 10 mg once daily maintenance dose) for a median of 14.5 months (5802 patients were treated for over 6 months, 4136 patients were treated for more than 1 year). The rate of study drug discontinuation due to adverse events was 7.2% for prasugrel and 6.3% for clopidogrel. Of these, bleeding was the most common adverse reaction for both drugs leading to study drug discontinuation (2.5% for prasugrel and 1.4% for clopidogrel).

Bleeding

Non-Coronary Artery Bypass Graft (CABG) related bleeding

In TRITON, the frequency of patients experiencing a non-CABG related bleeding event is shown in Table 1. The incidence of Non-CABG-related TIMI major bleeding, including life-threatening and fatal, as well as TIMI minor bleeding, was statistically significantly higher in subjects treated with prasugrel compared to clopidogrel in the UA/NSTEMI and All ACS populations. No significant difference was seen in the STEMI population. The most common site of spontaneous bleeding was the gastrointestinal tract (1.7% rate with prasugrel and 1.3% rate with clopidogrel); the most frequent site of provoked bleeding was the arterial puncture site (1.3% rate with prasugrel and 1.2% with clopidogrel).

Table 1: Incidence of Non-CABG related bleeding* (% Patients)

Event	All ACS		UA/NSTEMI		STEMI	
	Prasugrel ^a +ASA (N=6741)	Clopidogrel ^b +ASA (N=6716)	Prasugrel ^a +ASA (N=5001)	Clopidogrel ^b +ASA (N=4980)	Prasugrel ^a +ASA (N=1740)	Clopidogrel ^b +ASA (N=1736)
TIMI major bleeding ^c	2.2	1.7	2.2	1.6	2.2	2.0
Life-threatening ^d	1.3	0.8	1.3	0.8	1.2	1.0
Fatal	0.3	0.1	0.3	0.1	0.4	0.1
Symptomatic ICH ^e	0.3	0.3	0.3	0.3	0.2	0.2
Requiring inotropes	0.3	0.1	0.3	0.1	0.3	0.2
Requiring surgical intervention	0.3	0.3	0.3	0.3	0.1	0.2
Requiring transfusion (≥4 units)	0.7	0.5	0.6	0.3	0.8	0.8
TIMI minor bleeding ^f	2.4	1.9	2.3	1.6	2.7	2.6

a Centrally adjudicated events defined by the Thrombolysis in Myocardial Infarction (TIMI) Study Group criteria.

b Other standard therapies were used as appropriate.

c Any intracranial haemorrhage or any clinically overt bleeding associated with a fall in haemoglobin ≥5 g/dL.

d Life-threatening bleeding is a subset of TIMI major bleeding and includes the types identified below. Patients may be counted in more than one row.

e ICH=intracranial haemorrhage.

f Clinically overt bleeding associated with a fall in haemoglobin of ≥3 g/dL but <5 g/dL.

Patients ≥ 75 years old

In the phase 3 clinical trial, non-CABG-related TIMI major or minor bleeding rates for patients in two age groups were as follows:

Age	Prasugrel	Clopidogrel
≥75 years (N=1785)	9.0% (1.0% fatal)	6.9% (0.1% fatal)
<75 years (N=11672)	3.8% (0.2% fatal)	2.9% (0.1% fatal)

Patients < 60 kg

In the phase 3 clinical trial, non-CABG-related TIMI major or minor bleeding rates for patients in two weight groups were as follows:

Weight	Prasugrel	Clopidogrel
<60 kg (N=664)	10.1% (0% fatal)	6.8% (0.3% fatal)
≥60 kg (N=12672)	4.2% (0.3% fatal)	3.3% (0.1% fatal)

Lactose

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take Effient.

4.5 Interaction with other medicinal products and other forms of interaction

Warfarin: Concomitant administration of Effient with coumarin derivatives other than warfarin has not been studied. Because of the potential for increased risk of bleeding, warfarin (or other coumarin derivatives) and prasugrel should be co-administered with caution (see section 4.4).

Non-steroidal anti-inflammatory drugs (NSAIDs): Concomitant administration with chronic NSAIDs has not been studied. Because of the potential for increased risk of bleeding, chronic NSAIDs (including COX-2 inhibitors) and Effient should be co-administered with caution (see section 4.4).

Effient can be concomitantly administered with medicinal products metabolised by cytochrome P450 enzymes (including statins), or medicinal products that are inducers or inhibitors of cytochrome P450 enzymes. Effient can also be concomitantly administered with ASA, heparin, digoxin, and medicinal products that elevate gastric pH, including proton pump inhibitors and H₂ blockers. Although not studied in specific interaction studies, Effient has been co-administered in the phase 3 clinical trial with low molecular weight heparin, bivalirudin, and GP IIb/IIIa inhibitors (no information available regarding the type of GP IIb/IIIa inhibitor used) without evidence of clinically significant adverse interactions.

In patients ≥ 60 kg and age < 75 years, non-CABG-related TIMI major or minor bleeding rates were 3.6% for prasugrel and 2.8% for clopidogrel; rates for fatal bleeding were 0.2% for prasugrel and 0.1% for clopidogrel.

CABG-related bleeding

In the phase 3 clinical trial, 437 patients underwent CABG during the course of the study. Of those patients, the rate of CABG-related TIMI major or minor bleeding was 14.1% for the prasugrel group and 4.5% in the clopidogrel group. The higher risk for bleeding events in subjects treated with prasugrel persisted up to 7 days from the most recent dose of study drug. For patients who received their thienopyridine within 3 days prior to CABG, the frequencies of TIMI major or minor bleeding were 26.7% (12 of 45 patients) in the prasugrel group, compared with 5.0% (3 of 60 patients) in the clopidogrel group. For patients who received their last dose of thienopyridine within 4 to 7 days prior to CABG, the frequencies decreased to 11.3% (9 of 80 patients) in the prasugrel group and 3.3% (3 of 90 patients) in the clopidogrel group. Beyond 7 days after drug discontinuation, the observed rates of CABG-related bleeding were similar between treatment groups (see section 4.4).

Adverse Reactions

Table 2 summarises haemorrhagic and non-haemorrhagic adverse reactions in TRITON classified by frequency and system organ class. Frequencies are defined as follows:

Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1000$ to $< 1/100$);

rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); not known (cannot be estimated from the available data).

Table 2: Haemorrhagic and Non-haemorrhagic adverse reactions

System Organ Class	Common	Uncommon	Rare
Blood and Lymphatic System Disorders	Anaemia		
Eye Disorders		Eye haemorrhage	
Vascular Disorders	Haematoma		
Respiratory, Thoracic and Mediastinal Disorders	Epistaxis	Haemoptysis	
Gastrointestinal Disorders	Gastrointestinal haemorrhage	Retropertitoneal haemorrhage Rectal haemorrhage Haematochezia Gingival bleeding	
Skin and Subcutaneous Tissue Disorders	Rash Echymosis		
Renal and Urinary Disorders	Haematuria		
General Disorders and Administration Site Conditions	Vessel puncture site haematoma Puncture site haemorrhage		
Injury, Poisoning and Procedural Complications	Contusion	Post-procedural haemorrhage	Subcutaneous haematoma

In patients with or without a history of TIA or stroke, the incidence of stroke in the phase 3 clinical trial was as follows (see section 4.4):

History of TIA or stroke	Prasugrel	Clopidogrel
Yes (N=618)	6.5% (2.3% ICH*)	1.2% (0% ICH*)
No (N=13090)	0.9% (0.2% ICH*)	1.0% (0.3% ICH*)

* ICH=intracranial haemorrhage.

4.9 Overdose

Overdose of Effient may lead to prolonged bleeding time and subsequent bleeding complications. No data are available on the reversal of the pharmacological effect of prasugrel; however, if prompt correction of prolonged bleeding time is required, platelet transfusion and/or other blood products may be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Not yet assigned. ATC code: Not yet assigned.

Pharmacodynamics

Prasugrel is an inhibitor of platelet activation and aggregation through the irreversible binding of its active metabolite to the P2Y₁₂ class of ADP receptors on platelets. Since platelets participate in the initiation and/or evolution of thrombotic complications of atherosclerotic disease, inhibition of platelet function can result in the reduction of the rate of cardiovascular events such as death, myocardial infarction, or stroke.

Following a 60 mg loading dose of prasugrel, inhibition of ADP-induced platelet aggregation occurs at 15 minutes with 5 µM ADP and 30 minutes with 20 µM ADP. The maximum inhibition by prasugrel of ADP-induced platelet aggregation is 83% with 5 µM ADP and 79% with 20 µM ADP, in both cases with 99% of healthy subjects and patients with stable atherosclerosis achieving at least 50% inhibition of platelet aggregation by 1 hour. Prasugrel-mediated inhibition of platelet aggregation exhibits low between-subject (12%) and within-subject (9%) variability with both 5 µM and 20 µM ADP. Mean steady-state inhibition of platelet aggregation was 74% and 69% respectively for 5 µM ADP and 20 µM ADP, and was achieved following 3 to 5 days of administration of the 10 mg prasugrel maintenance dose preceded by a 60 mg loading dose. More than 98% of subjects had ≥20% inhibition of platelet aggregation during maintenance dosing.

Platelet aggregation gradually returned to baseline values after treatment in 7 to 9 days after administration of a single 60 mg loading dose of prasugrel and in 5 days following discontinuation of maintenance dosing at steady-state.

Clopidogrel: Following administration of 75 mg clopidogrel once daily for 10 days, 40 healthy subjects were switched to prasugrel 10 mg once daily with or without a loading dose of 60 mg. Similar or higher inhibition of platelet aggregation was observed with prasugrel. Switching directly to prasugrel 60 mg loading dose resulted in the most rapid onset of higher platelet inhibition. Following administration of a 900 mg loading dose of clopidogrel (with ASA), 56 subjects with ACS were treated for 14 days with either prasugrel 10 mg once daily or clopidogrel 150 mg once daily, and then switched to either clopidogrel 150 mg or prasugrel 10 mg for another 14 days. Higher inhibition of platelet aggregation was observed in patients switched to prasugrel 10 mg compared with those treated with clopidogrel 150 mg. No data are available on switching from a clopidogrel loading dose directly to a prasugrel loading dose.

Efficacy and Safety in Acute Coronary Syndrome (ACS)

The phase 3 TRITON study compared Effient (prasugrel) with clopidogrel, both co-administered with ASA and other standard therapy. TRITON was a 13,608 patient, multicentre international, randomised, double blind, parallel group study. Patients had ACS with moderate to high risk UA, NSTEMI, or STEMI and were managed with PCI.

Patients with UA/NSTEMI within 72 hours of symptoms or STEMI between 12 hours to 14 days of symptoms were randomised after knowledge of coronary anatomy. Patients with STEMI within 12 hours of symptoms and planned for primary PCI could be randomised without knowledge of coronary anatomy. For all patients, the loading dose could be administered anytime between randomisation and 1 hour after the patient left the catheterisation lab.

Patients randomised to receive prasugrel (60 mg loading dose followed by 10 mg once daily) or clopidogrel (300 mg loading dose followed by 75 mg once daily) were treated for a median of 14.5 months (maximum of 15 months with a minimum of 6 months follow-up). Patients also received ASA (75 mg to 325 mg once daily). Use of any thienopyridine within 5 days before enrolment was an exclusion criterion. Other therapies, such as heparin and GPIIb/IIIa inhibitors, were administered at the discretion of the physician. Approximately 40% of patients (in each of the treatment groups) received GPIIb/IIIa inhibitors in support of PCI (no information available regarding the type of GPIIb/IIIa inhibitor used). Approximately 98% of patients (in each of the treatment groups) received antithrombins (heparin, low molecular weight heparin, bivalirudin, or other agent) directly in support of PCI.

The trial's primary outcome measure was the time to first occurrence of cardiovascular (CV) death, non-fatal myocardial infarction (MI), or non-fatal stroke. Analysis of the composite endpoint in the All ACS population (combined UA/NSTEMI and STEMI cohorts) was contingent on showing statistical superiority of prasugrel versus clopidogrel in the UA/NSTEMI cohort (p<0.05).

All ACS population: Effient showed superior efficacy compared to clopidogrel in reducing the primary composite outcome events as well as the pre-specified secondary outcome events, including stent thrombosis (see Table 3). The benefit of prasugrel was apparent within the first 3 days and it persisted to the end of study. The superior efficacy was accompanied by an increase in major bleeding (see sections 4.4 and 4.8). The patient population was 92% Caucasian, 28% female, and 39% ≥65 years of age. The benefits associated with prasugrel were independent of the use of other acute and long-term cardiovascular therapies, including heparin/low molecular weight heparin, bivalirudin, intravenous GPIIb/IIIa inhibitors, lipid-lowering medicinal products, beta-blockers, and angiotensin converting enzyme inhibitors. The efficacy of prasugrel was independent of the ASA dose (75 mg to 325 mg once daily). The use of oral anticoagulants, non-study antiplatelet medicinal products and chronic NSAIDs was not allowed in TRITON. In the All ACS population, prasugrel was associated with a lower incidence of CV death, non-fatal MI, or non-fatal stroke compared to clopidogrel, regardless of baseline characteristics such as age, sex, body weight, geographical region, use of GPIIb/IIIa inhibitors, and stent type. The benefit was primarily due to a significant decrease in non-fatal MI (see table 3). Subjects with diabetes had significant reductions in the primary and all secondary composite endpoints.

The observed benefit of prasugrel in patients ≥ 75 years was less than that observed in patients <75 years. Patients ≥ 75 years were at increased risk of bleeding, including fatal (see sections 4.2, 4.4, and 4.8). Patients ≥ 75 years in whom the benefit with prasugrel was more evident included those with diabetes, STEMI, higher risk of stent thrombosis, or recurrent events.

Patients with a history of TIA or a history of ischaemic stroke more than 3 months prior to prasugrel therapy had no reduction in the primary composite endpoint.

Table 3: Patients with Outcome Events in TRITON Primary Analysis

Outcome Events	Prasugrel + ASA (N=6813) %	Clopidogrel + ASA (N=6705) %	Hazard Ratio (HR) (95% CI)	p-value
All ACS			0.812 (0.732, 0.902)	<0.001
Primary Composite Outcome Events Cardiovascular (CV) death, non fatal MI, or non fatal stroke	9.4	11.5		
Primary Individual Outcome Events				
CV death	2.0	2.2	0.886 (0.701, 1.118)	0.307
Nonfatal MI	7.0	9.1	0.757 (0.672, 0.853)	<0.001
Nonfatal stroke	0.9	0.9	1.018 (0.712, 1.451)	0.930
UA/NSTEMI				
Primary Composite Outcome Events	(N=5044) %	(N=5030) %		
CV death, nonfatal MI, or nonfatal stroke	9.3	11.2	0.820 (0.726, 0.927)	0.002
CV death	1.8	1.8	0.979 (0.732, 1.309)	0.885
Nonfatal MI	7.1	9.2	0.761 (0.683, 0.873)	<0.001
Nonfatal stroke			0.979 (0.633, 1.513)	0.922
STEMI				
Primary Composite Outcome Events	(N=1769) %	(N=1765) %		
CV death, nonfatal MI, or nonfatal stroke	9.8	12.2	0.793 (0.649, 0.968)	0.019
CV death	2.4	3.3	0.738 (0.497, 1.094)	0.129
Nonfatal MI	6.7	8.8	0.748 (0.558, 0.948)	0.016
Nonfatal stroke	1.2	1.1	1.097 (0.590, 2.040)	0.770

Prasugrel was associated with a 50% reduction in stent thrombosis through the 15 month follow-up period. The reduction in stent thrombosis with Effient was observed both early and beyond 30 days for both bare metal and drug eluting stents.

In an analysis of patients who survived an ischaemic event, prasugrel was associated with a reduction in the incidence of subsequent primary endpoint events (7.8% for prasugrel vs 11.9% for clopidogrel).

Although bleeding was increased with prasugrel, an analysis of the composite endpoint of death from any cause, nonfatal myocardial infarction, nonfatal stroke, and non-CABG-related TIMI major haemorrhage favoured Effient compared to clopidogrel (Hazard ratio, 0.87; 95% CI, 0.79 to 0.95; p=0.004). In TRITON, for every 1000 patients treated with Effient, there were 22 fewer patients with myocardial infarction, and 5 more with non-CABG-related TIMI major haemorrhages, compared with patients treated with clopidogrel.

5.2 Pharmacokinetic properties

Prasugrel is a prodrug and is rapidly metabolised in vivo to an active metabolite and inactive metabolites. The active metabolite's exposure (AUC) has moderate to low between-subject (27%) and within-subject (19%) variability. Prasugrel's pharmacokinetics are similar in healthy subjects, patients with stable atherosclerosis, and patients undergoing percutaneous coronary intervention.

Absorption

The absorption and metabolism of prasugrel are rapid, with peak plasma concentration (C_{max}) of the active metabolite occurring in approximately 30 minutes. The active metabolite's exposure (AUC) increases proportionally over the therapeutic dose range. In a study of healthy subjects, AUC of the active metabolite was unaffected by a high fat, high calorie meal, but C_{max} was decreased by 49% and the time to reach C_{max} (T_{max}) was increased from 0.5 to 1.5 hours. Effient was administered without regard to food in TRITON. Therefore, Effient can be administered without regard to food; however, the administration of prasugrel loading dose in the fasted state may provide most rapid onset of action (see section 4.2).

Distribution

Active metabolite binding to human serum albumin (4% buffered solution) was 98%.

Metabolism

Prasugrel is not detected in plasma following oral administration. It is rapidly hydrolysed in the intestine to a thiolactone, which is then converted to the active metabolite by a single step of cytochrome P450 metabolism, primarily by CYP3A4 and CYP2B6 and to a lesser extent by CYP2C9 and CYP2C19. The active metabolite is further metabolised to two inactive compounds by S-methylation or conjugation with cysteine.

In healthy subjects, patients with stable atherosclerosis, and patients with ACS receiving Effient, there was no relevant effect of genetic variation in CYP3A5, CYP2B6, CYP2C9, or CYP2C19 on the pharmacokinetics of prasugrel or its inhibition of platelet aggregation.

Elimination

Approximately 68% of the prasugrel dose is excreted in the urine and 27% in the faeces, as inactive metabolites. The active metabolite has an elimination half-life of about 7.4 hours (range 2 to 15 hours).

Special Populations:

Elderly: In a study of healthy subjects between the ages of 20 and 80 years, age had no significant effect on pharmacokinetics of prasugrel or its inhibition of platelet aggregation. In the large phase 3 clinical trial, the mean estimated exposure (AUC) of the active metabolite was 19% higher in very elderly patients (≥75 years of age) compared to subjects <75 years of age. Prasugrel should be used with caution in patients ≥ 75 years of age due to the potential risk of bleeding in this population (see sections 4.2 and 4.4).

Hepatic impairment: No dose adjustment is necessary for patients with mild to moderate impaired hepatic function (Child Pugh Class A and B). Pharmacokinetics of prasugrel and its inhibition of platelet aggregation were similar in subjects with mild to moderate hepatic impairment compared to healthy subjects. Pharmacokinetics and pharmacodynamics of prasugrel in patients with severe hepatic impairment have not been studied. Prasugrel must not be used in patients with severe hepatic impairment (see section 4.3).

Renal impairment: No dosage adjustment is necessary for patients with renal impairment, including patients with end stage renal disease (ESRD). Pharmacokinetics of prasugrel and its inhibition of platelet aggregation are similar in patients with moderate renal impairment (GFR 30–<50 ml/min/1.73m²) and healthy subjects. Prasugrel-mediated inhibition of platelet aggregation was also similar in patients with ESRD who required haemodialysis compared to healthy subjects, although C_{max} and AUC of the active metabolite decreased 51% and 42%, respectively, in ESRD patients.

Body weight: The mean exposure (AUC) of the active metabolite of prasugrel is approximately 30 to 40% higher in healthy subjects and patients with a body weight of <60 kg compared to those weighing ≥60 kg. Prasugrel should be used with caution in patients with a body weight of <60 kg due to the potential risk of bleeding in this population (see section 4.4).

Ethnicity: In clinical pharmacology studies, after adjusting for body weight, the AUC of the active metabolite was approximately 19% higher in Chinese, Japanese, and Korean subjects compared to that of Caucasians, predominantly related to higher exposure in Asian subjects <60 kg. There is no difference in exposure among Chinese, Japanese, and Korean subjects. Exposure in subjects of African and Hispanic descent is comparable to that of Caucasians. No dose adjustment is recommended based on ethnicity alone.

Gender: In healthy subjects and patients, the pharmacokinetics of prasugrel are similar in men and women.

Children and adolescents: Pharmacokinetics and pharmacodynamics of prasugrel have not been evaluated in a paediatric population (see section 4.2).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeat-dose toxicity, genotoxicity, carcinogenic potential, or toxicity to reproduction. 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.

Embryo-foetal developmental toxicology studies in rats and rabbits showed no evidence of malformations due to prasugrel. At a very high dose (>240 times the recommended daily human maintenance dose on a mg/m² basis) that caused effects on maternal body weight and/or food consumption, there was a slight decrease in offspring body weight (relative to controls). In pre- and post-natal rat studies, maternal treatment had no effect on the behavioural or reproductive development of the offspring at doses up to an exposure 240 times the recommended daily human maintenance dose (based on mg/m²).

No compound-related tumours were observed in a 2-year rat study with prasugrel exposures ranging to greater than 75 times the recommended therapeutic exposures in humans (based on plasma exposures to the active and major circulating human metabolites). There was an increased incidence of tumours (hepatocellular adenomas) in mice exposed for 2 years to high doses (>75 times human exposure), but this was considered secondary to prasugrel-induced enzyme-induction. The rodent-specific association of liver tumours and drug-induced enzyme induction is well documented in the literature. The increase in liver tumours with prasugrel administration in mice is not considered a relevant human risk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core:
Microcrystalline cellulose
Mannitol (E421)
Croscarmellose sodium
Hypromellose (E464)
Magnesium stearate

Effient 5 mg Film-Coat:
Lactose monohydrate
Hypromellose (E464)
Titanium dioxide (E171)
Triacetin (E1518)
Iron oxide yellow (E172)
Talc

Effient 10 mg Film-Coat:
Lactose monohydrate
Hypromellose (E464)
Titanium dioxide (E171)
Triacetin (E1518)
Iron oxide red (E172)
Iron oxide yellow (E172)
Talc

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Store in the original package to protect from air and moisture. Do not store above 30°C.

6.5 Nature and contents of container

Aluminum foil blisters in cartons of 14, 28, 30 (x1), 56, 84, 90 (x1) and 98 tablets.
Not all pack sizes may be marketed.

In the All ACS population, analysis of each of the secondary endpoints showed a significant benefit ($p < 0.001$) for prasugrel versus clopidogrel. These included definite or probable stent thrombosis at study end (0.9% vs 1.8%; HR 0.498; CI 0.364, 0.683); CV death, nonfatal MI, or urgent target vessel revascularisation through 30 days (5.9% vs 7.4%; HR 0.784; CI 0.688, 0.894); all cause death, nonfatal MI, or nonfatal stroke through study end (10.2% vs 12.1%; HR 0.831; CI 0.751, 0.919); CV death, nonfatal MI, nonfatal stroke or rehospitalisation for cardiac ischaemic event through study end (11.7 % vs 13.8%; HR 0.838; CI 0.762, 0.921). Analysis of all cause death did not show any significant difference between prasugrel and clopidogrel in the All ACS population (2.76% vs 2.90%), in the UA/NSTEMI population (2.58% vs 2.41%), and in the STEMI population (3.28% vs 4.31%).

6.6 Special precautions for disposal

No special requirements.

Manufactured by:

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PA0201SPXSP