리포락셀액(파클리탁셀)_(50mg/5mL),(0.1g/10mL),(0.3g/30mL)(대화제약(주))

가. 약제 정보

구 분	내 용
심의 대상 구분	재평가신청(재결정신청)
주성분 함량	1병 중 paclitaxel 50mg, 100mg, 300mg(10mg/ml)
제형 및 성상	냉장에서 흰색 또는 미황색의 반고체이며, 30℃ 이상에서는 무색 또는 미황색의 투명한 액이 무색 투명한 유리용기에 든 액제
효능·효과	진행성 및 전이성 또는 국소 재발성 위암
용법·용량	이 약은 28일(4주)를 주기로 3주간 투여 후 1주 휴약한다. 매주기 제 1, 8, 15일에 1일 2회(아침, 저녁) 식후 1시간 경과 후 1회 200mg/m^2 복용한다. 과민반응 예방을 위한 예비 투약은 필요 없다. 체표면적에 따른 1회 투여량과 용량 조정에 따른 투여량은 아래 표 <체표면적에 의한 용량 계산 및 감량 시 투여량>에 따른다.

<체표면적에 의한 용량 계산 및 감량 시 투여량>

용량 1회 200mg/m^2					1차 감량(75%) 1회 150mg/m^2	2차 감량(56%) 1회 112.5mg/m^2
체표면적 (m^2)	1회 투여량(mg)	투여 바이알 수				
		30mL	10mL	5mL	1회 투여량(mg)	1회 투여량(mg)
≤1.37	250	0	2	1	200	150
1.38~1.62	300	1	0	0	250	150
1.63~1.87	350	1	0	1	300	200
1.88≤	400	1	1	0	300	200

1. 용량조절

주기 시작 시점에는 호중구 수 1,500 cell/mm3 이상, 혈소판 수 100,000 cell/mm3 이상을 만족해야 치료를 시작할 수 있으며 충족되지 않는 경우 투여를 연기한다.

약물 복용 시에는 환자들에게 독성이 나타나는지 주의하여 모니터해야 한다. 이 약의 투여에 의한 독성은 대증 치료, 투약 일시 중단 및 용량 조정에 의해 조절될 수도 있다. 한 번 감량을 경험한 환자는 추후에 증량하지 않는다.

2. 투여방법

이 약은 냉장보관 (2~8℃)하였다가 투여 전부터 실온 (1~30℃)에서 보관이 가능하며 (최대 30일), 투여 전 체온을 이용해 충분히 데운 상태에서 내용물이 완전히 투명해 짐을 확인한 후 빨대 등을 이용해 복용한다.

	약물 투여 후 오심, 구토 등으로 인하여 정해진 용량이 모두 투여되지 않았더라도 재투약해서는 안되며 만약 아침 약물 투여 후 오심, 구토 등으로 저녁 투약이 어려울 경우는 다음날 아침 투여한다. 이 약 복용 후 30분 간은 가급적이면 물의 섭취를 제한하고 부득이 한 경우 한 컵(200cc정도) 이하의 물을 섭취하도록 권장한다.
의약품 분류	421 (항악성종양제), 전문의약품
품목허가일	2016년 9월 9일

나. 주요내용

(1) 대상 질환의 특성

▢ 위암

○ 국내 발생 및 유병 현황

- 국내에서 발생률이 가장 높은 암종이며, 유병률은 갑상선 암에 이어 2위인 암종임(2016년 기준)[1].
  - 2016년 위암은 30,504명에서 발생하여 전체 암 발생 환자의 13.3%를 차지하였고, 위암 환자는 116,870명으로(5년 유병 현황 기준) 전체 암환자의 14.2%를 차지함.
- 다른 조직으로 전이되었을 경우 5년 상대생존률은 5.9%로 매우 낮음.

▢ 진행성 및 전이성 위암의 치료

○ NCCN Guidelines Version 4.2019. Gastric Cancer

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2019
Gastric Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY

Systemic Therapy for Unresectable Locally Advanced, Recurrent or Metastatic Disease (where local therapy is not indicated)

- Trastuzumab[a] should be added to first-line chemotherapy for HER2 overexpressing metastatic adenocarcinoma (See Principles of Pathologic Review and Biomarker Testing [GAST-B])
  - Combination with fluoropyrimidine and platinum (category 1 in combination with cisplatin;[11] category 2A in combination with other platinum agents)
  - Trastuzumab is not recommended for use with anthracyclines

First-Line Therapy
- Two-drug cytotoxic regimens are preferred because of lower toxicity.
- Three-drug cytotoxic regimens should be reserved for medically fit patients with good PS and access to frequent toxicity evaluation.

Preferred Regimens
- Fluoropyrimidine (fluorouracil[c] or capecitabine) and oxaliplatin[12-14]
- Fluoropyrimidine (fluorouracil[c] or capecitabine) and cisplatin[12, 15-17]

Other Recommended Regimens
- Fluorouracil[c,f] and irinotecan[18]
- Paclitaxel with cisplatin or carboplatin[19-21]
- Docetaxel with cisplatin[22,23]
- Fluoropyrimidine[16,24,25] (fluorouracil[c] or capecitabine)
- Docetaxel[26,27]
- Paclitaxel[28,29]
- DCF modifications
  - Docetaxel, cisplatin, and fluorouracil[c,30]
  - Docetaxel, oxaliplatin, and fluorouracil[31]
  - Docetaxel, carboplatin, and fluorouracil (category 2B)[32]
- ECF (epirubicin, cisplatin, and fluorouracil) (category 2B)[33]
- ECF modifications (category 2B)[34,35]
  - Epirubicin, oxaliplatin, and fluorouracil
  - Epirubicin, cisplatin, and capecitabine
  - Epirubicin, oxaliplatin, and capecitabine

1) 국가암등록사업 연례 보고서 2016년 암등록통계, 2018.12, 보건복지부,중앙암등록본부,국립암센터

PRINCIPLES OF SYSTEMIC THERAPY

Systemic Therapy for Unresectable Locally Advanced, Recurrent or Metastatic Disease (where local therapy is not indicated)

Second-Line or Subsequent Therapy • Dependent on prior therapy and PS
Preferred Regimens • Ramucirumab and paclitaxel (category 1)[36] • Docetaxel (category 1)[25,26] • Paclitaxel (category 1)[27,28,37] • Irinotecan (category 1)[37-40] • Trifluridine and tipiracil (category 1)[41] ▸ For third-line or subsequent therapy • Fluorouracil[c,f] and irinotecan[38,42,43] • Pembrolizumab ▸ For second-line or subsequent therapy for MSI-H or dMMR tumors[44,45] ▸ For third-line or subsequent therapy for gastric adenocarcinoma with PD-L1 expression levels by CPS of ≥1[9,46]
Other Recommended Regimens • Ramucirumab (category 1)[47] • Irinotecan and cisplatin[13,48] • Entrectinib or Larotrectinib for *NTRK* gene fusion-positive tumors[49,50] • Docetaxel and irinotecan (category 2B)[51]

- HER2 양성인 환자의 일차요법시, 항암화학치료제에 trastuzumab을 함께 투여할 것이 권고됨.
- 일차요법으로서 fluoropyrimidine과 platinum의 2제 병용요법이 권고됨.
- 그 외 일차요법으로서 taxane계와 platinum계, fluoropyrimidine 등의 단독 및 병용요법이 사용될 수 있음.
- 이차요법으로서 환자의 상태, 1차요법에 사용된 약제를 고려하여 약제를 결정하며 ramucirumab, docetaxel, paclitaxel, irinotecan, ramucirumab +paclitaxel이 권고됨.

○ Korean Practice Guideline for Gastric Cancer 2018: an Evidence-based, Multi-disciplinary Approach[2)]

First-line systemic therapy

Statement 18-1. Palliative first-line platinum/fluoropyrimidine combination is recommended in patients with locally advanced unresectable or metastatic gastric cancer if the patient's performance status and major organ functions are preserved (evidence: high, recommendation: strong for).

Statement 18-2. Palliative trastuzumab combined with capecitabine or fluorouracil plus cisplatin is recommended in patients with human epidermal growth factor receptor 2 (HER2) immunohistochemistry

2) Guideline Committee of the Korean Gastric Cancer Association (KGCA), Development Working Group & Review Panel, Korean Practice Guideline for Gastric Cancer 2018: an Evidence-based, Multi-disciplinary Approach, J Gastric Cancer. 2019 Mar;19(1):1-48

(IHC) 3+ or IHC 2+ and in situ hybridization (ISH) positive advanced gastric cancer(evidence: high, recommendation: strong for).

Second-line systemic therapy

Statement 19. Palliative second-line systemic therapy is recommended in patients with locally advanced unresectable or metastatic gastric cancer if the patient's performance status and major organ functions are preserved. Ramucirumab plus paclitaxel is preferably recommended and monotherapy with irinotecan, docetaxel, paclitaxel, or ramucirumab could also be considered (evidence: high, recommendation, strong for)

- Randomized trials and a meta-analysis have demonstrated the survival benefit of secondline palliative chemotherapy (with irinotecan or taxanes) compared to best supportive care alone for patients with locally advanced unresectable or metastatic gastric cancer (HR, 0.64; 95% CI, 0.52-0.79; P<0.001). Weekly paclitaxel resulted in a similar OS to that achieved with irinotecan in phase III trials. In addition, ramucirumab, a monoclonal antibody targeting VEGFR-2, was shown to significantly improve survival in 2 phase III double-blind placebo-controlled trials. In the REGARD trial, patients receiving ramucirumab had improvements in both OS and PFS compared to those in patients receiving placebo. Similarly, in the RAINBOW trial, the addition of ramucirumab to weekly paclitaxel significantly prolonged the median OS (9.6 vs. 7.4 months; HR, 0.807; 95% CI, 0.678-0.962; P=0.017) compared to that for paclitaxel plus placebo.

- Based on the available data, ramucirumab in combination with paclitaxel is recommended as the most preferred second-line treatment. Irinotecan, docetaxel, paclitaxel, or ramucirumab as single agents can also be considered as a second-line option if not previously administered in the first-line treatment.

Third-line systemic therapy

Statement 20. Palliative third-line systemic therapy is recommended in patients with locally advanced unresectable or metastatic gastric cancer if the patient's performance status and major organ functions are preserved (evidence: high, recommendation: strong for).

○ Pan-Asian adapted ESMO Clinical Practice Guidelines for the management of patients with metastatic gastric cancer: a JSMO-ESMO initiative endorsed by CSCO, KSMO, MOS, SSO and TOS[3)]

Management of advanced/metastatic disease

Recommendation 6: second-and further-line treatment

6a. Second-line chemotherapy with a taxane (docetaxel, paclitaxel), or irinotecan, or ramucirumab as a single agent or in combination with paclitaxel is recommended for patients who are of PS 0-1 [A = 100% and I, A].

6b. Similar efficacy has been demonstrated for weekly paclitaxel and irinotecan. This recommendation was to be removed and be replaced with the new revised 'recommendation 6b' below.

6b. In patients treated with chemotherapy which stopped before progression and who have not progressed within 3 months it may be appropriate to consider the reintroduction of the same drug combination as long as any toxicity issues havebeen resolved [A = 100% and IV, C].

6c. Nivolumab, pembrolizumab or trifluridine/tipiracil (FTD/TPI, TAS-102) should be considered as third- or furtherline treatment, if approved. Irinotecan or a taxane (if not used in the earlier lines) are also options for third-or further-line treatment [A = 100% and V, C]. Apatinib may also be considered but only in China [A = 100% and I, A].

All 12 Asian experts agreed with and accepted completely [A = 100%] 'recommendation 6a' and the deletion of 'recommendation 6b', with the proposal that patients with mGC who have progressed on first-line treatment are assigned to secondline treatment and care according to the treatment options presented in Figure 1. These options are based on the observations that irinotecan or docetaxel monotherapy have been shown to be superior to BSC in individual trials in both Western and Asian patients, and also in a meta-analysis. A randomised phase III trial directly comparing irinotecan and paclitaxel as second-line therapy in patients with advanced GC showed them to have similar efficacy. Whilst, nab-paclitaxel(not approved for GC except for Japan) has been shown to be noninferior to paclitaxel in an open-label, randomised phase III trial. However, paclitaxel plus ramucirumab is now the preferred second-line treatment option for

3) Muro et al, Pan-Asian adapted ESMO Clinical Practice Guidelines for the management of patients with metastatic gastric cancer: a JSMO-ESMO initiative endorsed by CSCO, KSMO, MOS, SSO and TOS, Annals of Oncology 30: 19-33, 2019

patients with mGC and an Eastern Cooperative Oncology Group (ECOG) PS of 0 or 1, based on the results of the phase III RAINBOW trial conducted across 27 countries worldwide, in which 35% of the patients were of Asian ethnicity (ESMO MCBS 2). A Japanese study has also investigated nab-paclitaxel and ramucirumab in a single arm phase II trial and reported promising activity. Ramucirumab monotherapy is also one of the second-line options (Figure 1) based on the results of the randomised phase III REGARD trial in which 16% of the patients were of Asian ethnicity (ESMO MCBS 1). Today, irinotecan or taxane monotherapy is considered an alternative second-line treatment option for patients with mGC who are not candidates for ramucirumab treatment or where ramucirumab is not available. The experts agreed completely [A = 100%] with the new revised 'recommendation 6b' that for patients treated with chemotherapy which was stopped before progression and who have not progressed within 3 months it may be appropriate to consider the reintroduction of the same drug combination.

(2) 약제 특성

○ 신청품은 "진행성 및 전이성 또는 국소 재발성 위암"에 허가받은 약제로 파클리탁셀을 경구 복용할 수 있도록 개발된 개량신약임.

- 파클리탁셀은 세포분열시 미세소관을 형성하는 역할을 담당하는 튜블린의 비정상적인 중합을 촉진하여 작용을 나타냄. 비정상적인 튜블린은 미세소관이 그 기능을 발휘할 수 없는 형태로 형성시키며, 이로 인하여 세포분열을 위한 정상적인 역할을 할 수 없게 됨[4].
- 신청품은 자체적인 가용화 기술을 적용하여, 난용성인 파클리탁셀을 경구제제로 개발한 약제로 기존 정맥투여제제 대비 편의성 개선이 예상됨.

(3) 교과서 및 임상진료지침

- 관련 교과서 및 가이드라인[5][6][7][8][9][10]에 신청품과 동일한 투여경로의 약제에 관한 언급은 없으나, 동일한 성분의 정맥투여제제에 대하여 위암에서 고식적 요법으로서, 이차 또는 그 이후 치료시 단독 또는 병용요법으로 사용할 수 있는 약제로 언급하고 있음.

---

4) Sakamoto_2009_Paclitaxel chemotherapy for the treatment of gastric cancer. Gastric Cancer (2009)12: 69-78

5) Abeloff's Clinical Oncology Sixth Edition, 2020

6) Goldman-Cecil Medicine Twenty-Fifth Edition, 2016

7) Current Medical Diagnosis & Treatment 2019, Fifty-eighth Edition,

8) NCCN guidelines, version 2.2019 > Gastric cancer.

9) Muro et al, Pan-Asian adapted ESMO Clinical Practice Guidelines for the management of patients with metastatic gastric cancer: a JSMO-ESMO initiative endorsed by CSCO, KSMO, MOS, SSO and TOS, Annals of Oncology 30: 19-33, 2019

10) Guideline Committee of the Korean Gastric Cancer Association (KGCA), Development Working Group & Review Panel, Korean Practice Guideline for Gastric Cancer 2018: an Evidence-based, Multi-disciplinary Approach, J Gastric Cancer. 2019 Mar;19(1):1-48

(4) 임상시험 결과

▢ 신청품의 임상문헌으로 단독요법에서 신청품과 IV paclitaxel의 비교임상시험 1편을 분석함.

○ 수술 불가능하며 fluoropyrimidine, platinum 치료에 실패한 위암 환자를 대상으로 신청품군(n=118)과 IV paclitaxel군(3주요법, n=118)으로 무작위배정하여 공개 비교한 국내 환자 대상의 임상시험 결과[11], 신청품은 IV paclitaxel 3주요법 대비 1차평가지표인 무진행생존에서 비열등성을 입증함.

- 무진행생존기간중앙값(per protocol)은 신청품군 3.0개월(95% CI 1.7-4.0개월), IV군 2.6개월(95% CI 1.8-2.8개월)이었으며 신청품의 HR 상한값은 1.13으로(HR 0.85, 95%CI 0.64-1.13) 비열등성 마진으로 설정한 1.25보다 낮아 비열등성을 입증함.

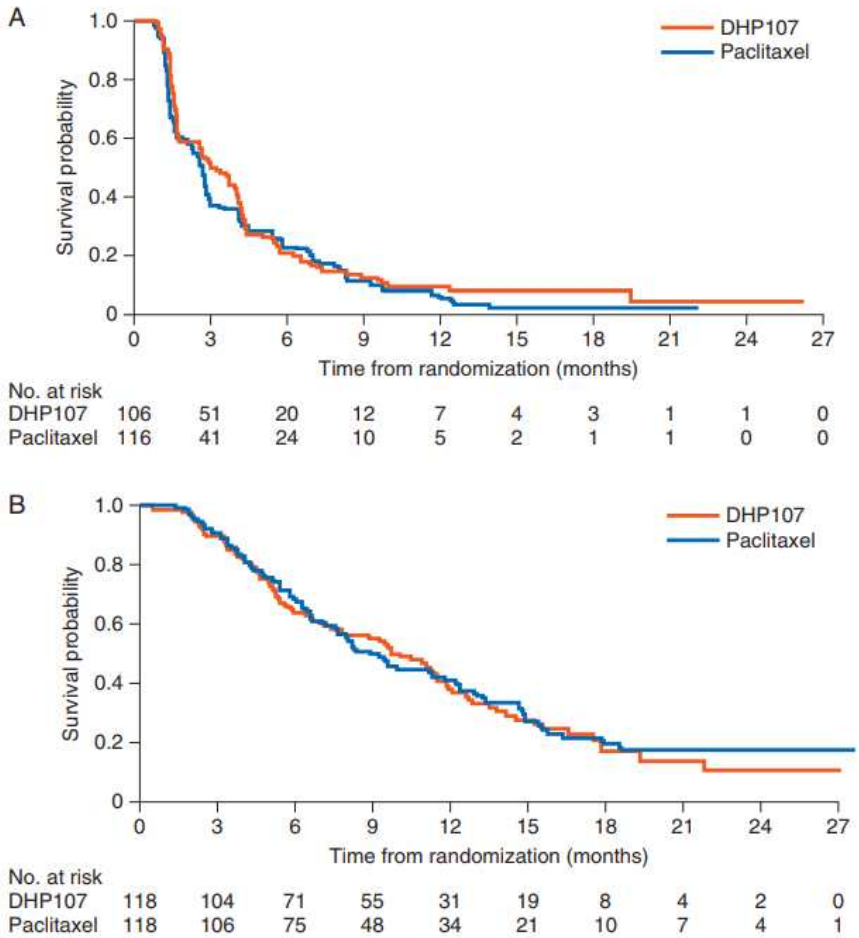

Figure 2. Progression-free survival (per-protocol population) (A) and overall survival (full analysis set) (B).

11) YK Kang et al, Efficacy and safety findings from DREAM: A phase III study of DHP107 (oral paclitaxel) vs IV paclitaxel in patients with advanced gastric cancer after failure of first-line chemotherapy, Annals of Oncology, 2018;29;1220-1226

- 전체생존기간의 중앙값은 신청품군 9.7개월(95% CI 7.1-11.5개월), IV군 8.9개월(95% CI 7.1-12.2개월)로 유사하였고, 반응률 또한 유사하였음.

Table 2. Tumor responses (full analysis set)

Response, *n* (%)	Oral DHP107 (*n* = 118)	i.v. paclitaxel (*n* = 118)
Investigator assessment		
Complete response	5 (4.2)	4 (3.4)
Partial response	16 (13.6)	26 (22.0)
Stable disease	42 (35.6)	40 (33.9)
Progressive disease	46 (39.0)	46 (39.0)
Not evaluable	9 (7.6)	2 (1.7)
Independent assessment		
Complete response	2 (1.7)	3 (2.5)
Partial response	20 (16.9)	17 (14.4)
Stable disease	42 (35.6)	50 (42.4)
Progressive disease	48 (40.7)	46 (39.0)
Not evaluable	6 (5.1)	2 (1.7)

i.v., intravenous.

(5) 학회의견

○ 관련 학회[12]에 따르면, 신청품은 기존 IV paclitaxel을 대조약으로 한 임상시험에서 무진행 생존기간의 비열등성을 입증하였고 OS도 유사하게 나타났으며, 부형제에 의한 과민반응이 없고 전처치 및 점적투여가 필요하지 않은 약제로, 환자에게 복용 편의성 측면에서 유리할 것으로 판단됨.

(6) 진료상 필수여부

○ 신청품은 "진행성 및 전이성 또는 국소 재발성 위암"에 허가 받은 약제로, 현재 해당 적응증에 사용가능한 약제로 IV paclitaxel, docetaxel 등이 등재되어 있어 대체 가능성 등을 고려 시, 약제의 요양급여대상여부 등의 평가기준 및 절차 등에 관한 규정 제6조(진료상 반드시 필요하다고 판단되는 약제)에 해당한다고 보기 어려움.

12) 한국임상암학회( ), 대한항암요법연구회( ), 대한암학회( )

(7) 제외국 약가집 수재 현황

○ 신청품은 paclitaxel의 유일한 경구제로, 국내 개발되어 제외국 허가, 등재, 평가 사례는 없음.