

디비엘 메토크렉세이트 주
DBL Methotrexate Inj.

■ 원료 약품의 분량 :

- 디비엘 메토크렉세이트 주 25mg/ml : 1ml 중
<주성분> 메토크렉세이트 (비 피) 25mg
<용 제> 주 사 용 수 (비 피) 적량
- 디비엘 메토크렉세이트 주 1g : 1바이알 (10ml) 중
<주성분> 메토크렉세이트 (비 피) 1g
<용 제> 주 사 용 수 (비 피) 적량
- 디비엘 메토크렉세이트 주 5g : 1바이알 (50ml) 중
<주성분> 메토크렉세이트 (비 피) 5g
<용 제> 주 사 용 수 (비 피) 적량

■ 성 상 : 투명한 바이알에 황색내지 미황색의 맑은 액이 들어있는 액상주사제

■ 효능·효과

1. 다음과 같은 암상태의 광범위한 처치
① 급성백혈병, 비호지킨림프종, 육종(연부육종, 골육종)
② 유방암, 폐암, 두경부암, 방광암의 고형암, 용모질환(용모암, 파괴포상기배, 포상기배)
2. 다른 약물로 효과가 없는 중증의 불응성 건선

■ 용법·용량

1. 각 적응증에 따른 투여량은 다음과 같다.
① 소아의 수막백혈병 : 1주 간격으로 뇌척수액이 정상으로 돌아올 때(일반적으로 2~3주) 까지 이 약으로서 12~15 mg/m²(약 체중 kg당 0.4~0.5 mg)을 수막강주사한다.
② 용모질환 : 5일을 1주기로 하여 1일 이 약으로서 10~30 mg/m²(적절히 중감)을 5일간 근육주사한다. 7~12일의 휴약 기간을 갖거나 이상반응이 가라앉을 때까지 휴약한다. 1주기를 3~5회 반복할 수 있다.
③ 유방암 : 이 약으로서 10~60 mg/m²을 정맥주사한다.
④ 폐암 : 이 약으로서 20~100 mg/m²을 정맥주입 또는 정맥주사한다.
⑤ 두경부암 : 이 약으로서 240~1,080 mg/m²을 정맥주입 후 로이코보린 칼슘 구원 요법을 실시한다.
⑥ 방광암 : 이 약으로서 최대 100 mg까지 1주 또는 2주마다 정맥주사 또는 정맥주입한다.
⑦ 골육종 : 이 약으로서 600~9,000 mg/m²을 정맥주입 후 로이코보린 칼슘 구원요법을 실시한다.
⑧ 비호지킨성 림프종 : 이 약으로서 90~900 mg/m²을 정맥주사 또는 정맥주입 후 고용량의 로이코보린 칼슘을 투여한다.
이상의 투여처방은 이 약의 단일투여 또는 종종 다른 약물과 병용되며, 다른 약물과의 병용 시 병용에 의한 독성증가를 고려하여 투여량을 감량해야 한다.
2. 건선에 대한 투여
성인 : 치료 1주일 전 1회 이 약으로서 5~10 mg의 시험용량을 경구투여 하여 특이체질의 이상반응 시험을 권장한다. 기존의 요법에 불응성인 심하고 통제 불가능한 건선에 대한 투여는 일반적으로 1주 1회 10~25 mg을 경구 투여하나, 정맥 또는 근육주사하기도 한다. 주사로 투여할 경우 환자의 반응에 따라 용량을 조절한다. 환자에게는 건선에 대한 이 약의 치료와 관련된 모든 위험을 알려주어야 하고, 임상적사는 이 약 치료를 하기 전 간기능 검사를 함으로써 간독성 발현에 주의를 기울여야 하며, 치료 동안 2~4개월 간격으로 간 기능검사를 반복한다. 간기능시험 또는 간생검결과 이상이 있으면 처치를 중단해야 한다. 이 치료의 목적은 가장 긴 휴약기간과 함께 가능한 최소 용량으로 감량하는데 있다. 이 약의 사용이 권장 치료법인 재래국소치료로의 전환을 가능하게 할 수 있다. 신장 손상 환자에게는 용량을 감량해야 한다.
백혈구, 혈소판 수가 임상학적으로 현저하게 떨어지면, 이 약의 사용은 즉시 중지하여야 한다. 이 약은 특히 고용량 또는 장기간 사용에서 간독성이 있을 수 있고, 간위축증, 괴사, 간경 화증, 지방변성, 문맥주위섬유증 등의 변화가 보고되었다. 이러한 변화는 위장관 독성 또는 혈액학적 독성이 사전 징후 없이도 일어날 수 있으므로 치료 전 간기능 검사와 치료 동안 지속적인 모니터링이 필수적이다.
3. 이 약은 단독으로 사용하거나 방사선 요법 및 외과적 요법과 병행된다. 투여량의 결정은 신중히 해야 한다. 로이코보린 구원요법과의 간헐적인 대량 요법이 실시된다.

■ 사용상의 주의사항

1. 경 고
메토크렉세이트, 플루오로우라실 교대요법은 고도의 위험성을 수반하므로 투여 중 및 투여 후 일정기간은 환자를 의사의 감독 하에 두어야 한다. 또한 긴급한 경우에는 충분히 조치 할 수 있는 의료시설 및 항암화학요법에 충분한 경험을 가진 의사로서 본 요법이 적절하 다고 판단되어지는 증례에 대해서만 한다. 더욱이 본 요법의 개시에 있어서는 효능·효과, 용법·용량, 사용상의 주의사항을 충분히 숙독해야 한다.
2. 다음 환자에는 투여하지 말 것.
① 이 약 성분에 대해 중증 과민반응의 병력이 있는 환자
② 신장에 환자
③ 간장에 환자
④ 흉수, 복수 등이 있는 환자(흉수, 복수 등의 장기간 저류시 독성이 증강될 수 있다.)
⑤ 다음과 같은 상태의 건선 또는 류마티스 관절염 환자
(1) 골수형성부전, 백혈구감소증, 혈소판감소증, 심한 빈혈과 같은 기존의 혈액질환 환자
(2) 면역결핍증의 명백한 또는 실험실적 증거가 있는 환자
⑥ 알코올중독, 알코올성 간질환, 만성적 간질환 환자
⑦ 임부 또는 임신하고 있을 가능성이 있는 여성 및 수유부
⑦ 아시테렌을 투여중인 환자(6. 상호작용항 참조)
3. 다음 환자에는 신중히 투여할 것.
① 설사 또는 궤양성 구내염 환자(강진공으로 인한 출혈성 장염과 사망을 초래할 수 있다.)
② 위궤양 또는 궤양성 대장염 환자
③ 혈액학적 이상, 악성 또는 기존의 조혈 손상 환자
④ 골수기능억제 환자
⑤ 수도 환자(지명적인 전신장애가 나타날 수 있다.)
⑥ 감염증의 합병증이 있는 환자
⑦ 정신적 장애 환자
⑧ 소아
⑨ 고령자
4. 이상반응
① 속 : 드물게 속, 아나필락시스양 증상(냉감, 호흡곤란, 혈압하락 등)이 나타날 수 있으 므로 관찰을 충분히 하여 이상이 확인되는 경우에는 투여를 중지하고 적절한 처치를 한다.
② 소화기계
(1) 출혈성장염, 괴사성장염 등 중증 장염이 나타날 수 있으므로 충분히 관찰하고, 복통, 설사 등의 증상이 나타나면 투여를 중지하고 적절한 처치를 한다.
(2) 구역, 구토, 구내염, 식욕부진, 설염, 구진종창, 소화관궤양·출혈, 혈변, 장폐색이 나타날 수 있으므로 증상에 따라 적절한 처치를 한다.
(3) 궤장염이 나타날 수 있으므로 충분히 관찰하고, 복통, 설사 등의 증상이 나타나면 환자의 상태를 충분히 관찰하여 이상이 확인되면 투여를 중지하고 적절한 처치를 한다.
③ 호흡기계 : 간질성폐렴, 폐섬유증 등이 나타나면 관찰을 충분히 하고 발열, 기침, 호 흡곤란 등의 호흡기 증상이 나타났을 경우에는 즉시 흉부X선 검사 등을 실시하고, 이 약 투여를 중지함과 동시에 부신피질 호르몬제의 투여 등의 적절한 처치를 한다. 수막 강투여 후 급성 폐부종이 보고되었다.
④ 정신신경계 : 두통, 졸음, 시야흐림, 실어리즘, 불완전마비, 마비, 경련, 혼수, 치매, 경 부 및 둔근긴장, 동통증 등이 나타날 수 있다. 수막강투여 후 뇌척수액 압이 증가되었 고 경련, 불완전마비, 급성탈발단신경염(길랑-바레 증후군)이 나타날 수 있다.
⑤ 생식기계 : 무정자증, 난소기능부전, 월경부전, 불임, 유산, 태아기형, 질소혈중, 난 자생성 또는 정자발생 결손, 질염, 질궤양 등이 나타날 수 있다.
⑥ 혈액계 : 범혈구 감소, 무관립증상(전구증상으로서 발열, 인후통, 인플루엔자 유사 증 상이 나타날 수 있다.), 빈혈, 백혈구감소증, 혈소판감소증, 패혈증, 저감마글로불린 혈증 등의 골수억제 증상이 나타날 수 있다. 자주 혈액검사를 하는 등 환자의 상태를 충분히 관찰하고, 이상반응이 확인되면 감량, 휴약 등의 적절한 처치를 한다. 또한 과립 구감소증과 발열이 나타나면 즉시 검사를 하고 비경구용 광범위 항생제를 투여하는 등 적절한 처치를 한다.
⑦ 간장 : 중증 간염, 간장애(AST, ALT, ALP의 상승), 황달, 지방간, 간조적괴사 등의 증 상이 나타날 수 있으며 중증 간장애인 전격성간염, 간부전, 간조직 섬유화와 간경변 이 나타날 수 있으므로 이러한 경우 자주 간기능 검사를 하고, 이상이 확인되면 투여를 중지하는 등 적절한 처치를 한다. 만성투여로 인해 사망을 초래할 수 있다.
⑧ 신장 : 신부전, 방광염, 혈노, BUN 또는 크레아티닌치의 상승 등이 나타날 수 있다. 또 한 골육종 치료를 위해 투여된 이 약 고용량에 의해 급성신부전이 발생할 수 있다. 중증 신장애로서 급성신부전, 요새관괴사, 중증 신장병증이 나타날 수 있으므로 이러한 경우 자주 신기능 검사를 하고, 이상이 확인되면 투여를 중지하는 등 적절한 처치를 한다.
⑨ 과민반응 : 의식장애, 혈압강하, 빈맥, 마비감, 재채기, 호흡곤란, 흉부 불쾌감, 냉·발한 등 의 증상이 나타날 수 있으므로 이러한 증상이 나타나면 적절한 처치를 한다.
⑩ 피부 : 피부점막인종후근(스티븐스-존슨증후군), 중증성표피괴사용해(리얼증후군)가 나 타날 수 있으므로 충분히 관찰하고 광과민반응, 발열, 발진, 두드러기, 가려움, 홍반 성피진, 홍반, 색소침착, 탈색, 피부반상출혈, 여드름, 탈모, 모세혈관 확장증, 절창, 안진혈 등 이 나타나는 경우에는 투여를 중지하고 적절한 처치를 한다.
⑪ 감염증 : 뉴우모시스티스카리나 폐렴, 폐렴, 폐렴, 거대세포바이러스 감염증, 대상포 진 등 중증 감염증이 나타날 수 있으므로 환자의 상태를 충분히 관찰하고 이상이 확인 되면, 이 약의 투여 중지, 항생제, 항균제의 투여 등 적절한 처치를 한다.
⑫ 뼈 : 골다공증이 나타날 수 있으므로 환자를 충분히 관찰하고, 골밀도 감소 등의 이 상이 확인되면 투여를 중지하고 적절한 처치를 한다.
⑬ 기타 : 권태감, 이하선염, 결막염, 방광염, 관절염, 근육통, 당뇨병, 돌연사망 등이 나타날 수 있다.

5. 일반적 주의

- 1) 골수기능억제, 간·신기능검사, 요검사 등을 실시하는 등 환자의 상태를 충분히 관찰한다. 또한 이상이 나타나는 경우에는 감량, 휴약 등의 적절한 처치를 한다. 장기간 사용하는 경우 이상반응이 심하게 지속적으로 나타날 수 있으므로 신중히 투여해야 한다.
- 2) 감염증, 출혈경향 등의 발현, 또는 약화에 주의하여야 한다.
- 3) 소아 및 생식가능 연령의 환자에게 투여할 필요가 있는 경우에는 성선에 대한 영향을 고려한다.
- 4) 이 약 투여에 의한 신장장애는 주로 이 약의 성분과 7-hydroxy methotrexate의 결정이 신세뇨관에 침착되어 나타나는 것이므로 약물의 결정화를 방지하기 위해 요의 알칼리화, 충분한 수분공급, 요를 통한 배설 등을 고려하고 혈중농도와 혈청크레아티닌치의 측정 등을 세심하게 관찰한다.
- 5) 이 약 투여에 의해 유발된 폐질환은 위험한 장애가 될 수 있으며, 이는 치료 도중 어느 때에도 급성으로 나타날 수 있다. 7.5mg/week 의 저용량 투여에서도 보고된 바 있으며 이는 항상 완전하게 가역적인 것이 아니다. 또한 폐질환이 의심되는 경우 baseline measurement와 같은 폐기능 검사가 유용하다.
- 6) 저용량을 장기간 투여하는 경우 특히 간독성을 일으킬 수 있으므로 간기능 검사를 주기적으로 실시하고 이상이 나타나면 최소 2주간 투여를 중지한다.
- 7) 이 약은 정자 또는 난자 생성에 영향을 미쳐 생식 기능을 가역적으로 감소시킬 수 있으므로 최소한 이 약 투여 중지 후 6개월 동안은 임신을 피해야 한다.
- 8) 척수강내 투여 후 특히 뇌에 대한 방사선요법을 병용한 경우 백색질뇌증(Leucoencephalopathy)이 관찰되었다.
- 9) 이 약은 면역억제가능 기능을 지니므로 백신의 면역학적 반응을 감소시킬 수 있다. 생백신과 병용투여하는 경우 심한 항원반응이 발생할 수 있다.
- 10) 혈액 성분의 심한 감소가 나타나면 즉시 투여를 중지하고 수혈 또는 가역적 장벽 간호(reverse barrier nursing)와 같은 보조요법을 실시한다.
- 11) 저용량에서도 조혈인자(hemopoietin) 억제가 갑자기 나타날 수 있다.
- 12) 중추신경계에 대한 방사선요법 시 동시에 이 약을 척수강내로 투여하지 않는다. 척수강내 투여 후 체순환을 통해 전신 독성, 특히 골수억제가 나타날 수 있다.

6. 상호작용

- 1) 다음 약물과 병용투여하는 경우 신세뇨관에서의 메토포레이트 수송 기능이 감소되고 그 결과 배설이 지연되어 이 약의 작용이 증가될 수 있으므로 병용투여하는 경우에는 신중히 투여한다. : 설폰아미드계 약물, 테트라사이클린, 클로람페니콜, 페니토인, 바르비탈산 유도제, 아미노안식향산, 프로파온산, 소염제, 치아지드계 이뇨제, 프로베네시드, 설판페라존, 페니실린
- 2) 이 약은 광범위한 단백질 결합 능력을 가지고 있으며 이는 살리실산, 페닐부타존, 이노제, 당노병용제, 페니도인, 설폰아미드계, 테트라사이클린, 클로람페니콜, p-aminobenzoic acid, 산성 소염제의 병용에 의해 대체될 수 있으므로 독성이 증가될 수 있다.
- 3) 드물게 코트리목사졸은 이 약의 작용을 증가시킬 수 있으므로 주의한다.
- 4) 코트리목사졸 또는 트리메토프림의 동시 사용 후 중증 골수억제가 보고되었으므로 동시 사용을 권장하지 않는다.
- 5) 염산을 함유하는 비타민 제제 또는 염산 유도제는 이 약의 효능을 감소시킬 수 있다.
- 6) 임상적으로 필요하다고 고려될 경우를 제외하고(이런 경우 환자는 계속 모니터링하여야 한다.) 잠재적 신독성, 간독성(알코올을 포함)을 갖는 다른 약물과 이 약의 병용은 피해야 한다.
- 7) 프로베네시드에 의해 이 약의 신장 배설이 저해되므로 이 약의 이상반응(골수억제, 간·신장·소화관장애, 혈액 장애 등)이 증가될 수 있으므로 자주 임상검사를 하는 등 관찰을 충분히 하고 이상이 확인되면 감량·휴약 등의 적절한 처치를 한다. 또한 이 약의 길항제인 로이코보린을 투여한다.
- 8) 아산화질소의 병용 시 이 약으로 유발된 구내염과 다른 독성 효과가 증가될 수 있다.
- 9) 이 약과 acitretin 대사체(etretinate)의 병용이 간염의 위험을 증가시킨다고 보고 되었으므로 이 약과 acitretin을 병용투여하지 않는다.
- 10) 테르프로미드에 의해 이 약의 이상반응(골수억제, 간·신장·소화관장애, 혈액장애 등)이 증가될 수 있으므로 자주 임상검사를 하는 등 관찰을 충분히 하고 이상이 확인되면 감량·휴약 등의 적절한 처치를 한다. 또한 이 약의 길항제인 로이코보린을 투여한다.
- 11) 비스테로이드 소염제(NSAIDs) 및 살리실산 : 비스테로이드 소염제(NSAIDs) 및 살리실산과의 병용투여로 신세뇨관에서 이 약의 배설이 지연되어 치명적인 이 약의 혈액학적 독성이 증가될 수 있으므로 항암요법으로 사용하는 고용량의 이 약과는 병용투여하지 않으며, 저용량의 이 약과 병용투여 시 신중히 투여하여야 한다.
- 12) 아스피린 : 아스피린과의 병용투여로 신세뇨관에서 이 약의 배설이 지연되어 치명적인 이 약의 혈액학적 독성이 증가될 수 있으므로 고용량의 이 약(15mg/주 이상)을 투여할 경우 아스피린과 병용투여하지 않으며, 저용량의 이 약과 병용투여 시에는 신중히 투여하여야 한다.

7. 임부 및 수유부에 대한 투여

- 1) 특히 임신 1기에 이 약을 투여 받은 임부에서 유산, 태아사망 및/또는 선천기형이 나타남다. 임부의 진전 또는 류마티스관절염의 관리에서 이 약의 사용은 금기이다. 동물 실험에서 기형유발 작용이 보고되어 있으므로 임부 또는 임신하고 있을 가능성이 있는 여성에는 투여하지 않는다. 이 약을 투여 받은 환자에서서 난자형성 또는 정자발생 이상, 일시적 정자부족증, 월경기능장애, 불임증이 나타났다는 보고가 있다.
- 2) 이 약은 모유 중으로 분비되므로 수유부에게는 투여하지 않는다. 부득이하게 투여하는 경우에는 수유를 중지한다.

8. 소아에 대한 투여

미숙아, 신생아, 영아, 소아에 대한 안전성은 확립되어 있지 않다(사용경험이 적다).

9. 고령자에 대한 투여

고령자에 대한 임상 약리는 연구되지 않았으며 이들은 염산 저장량이 적고 간 및 신기능이 저하되어 있으므로 비교적 저용량을 투여하고 독성의 초기 표시에 대하여 자세히 모니터링 한다.

10. 임상검사치에의 영향

설폰아메톡사졸·트리메토프림 복합제를 병용투여할 경우 2수소염산환원효소(dihydrofolate reductase : DHFR)를 이용한 이 약의 농도 측정시 높은 수치를 나타낼 수 있으므로 주의해야 한다.

11. 과량투여시의 처리

부주의하여 과량투여된 이 약은 로이코보린에 의해 중화되고 독성이 감소될 수 있으므로 로이코보린을 즉시 주사한다. 동량 또는 그 이상으로 정맥주사하거나 일시(bolus) 주사한다. 이 약과 로이코보린 투여 간격이 클수록 독성을 경감시키는 로이코보린의 효과는 감소하므로 늦어도 1시간 이내에 투여한다. 특히 대량투여 시 로이코보린 투여 기간과 적정 용량을 결정하기 위하여 반드시 이 약의 혈중 농도를 측정한다. 대량투여의 경우에는 이 약과 이 약의 대사산물이 신세뇨관에 침착되는 것을 방지하기 위해 수분·공급과 요의 알칼리화를 한다. 혈액투석 또는 복막투석 모두 이 약을 제거시키지 못한다. 그러나 환자에 대하여 주의 깊게 관찰하여 수혈, 신장투석, 가역적 장벽 간호 등의 보조요법을 실시한다.

12. 적용상의 주의

1) 조제방법

- (1) 이 약 용액은 배합금기의 가능성이 있으므로 다른 의약품과 혼합해서는 안되며 특히 플루오로우라실, 프레드니솔론인산나트륨, 시타라빈과 혼합 시 흡수 스펙트럼의 변화가 관찰된다.
- (2) 이 약은 생리식염 주사액, 5% 포도당생리식염 주사액으로 희석하여 즉시 사용한다. 이때 최소 24시간 동안은 안정하며, 사용 후 남은 용액은 반드시 폐기한다.
- (3) 이 약과 보존제를 함유하는 희석제 사용은 수막강 투여와 고용량 치료에서는 금기이다.

2) 투여경로

- (1) 소량투여(정맥주사 또는 근육주사)
- (2) 대량투여(급속 정맥주사(i.v. bolus inj.)) 또는 주입(infusion)
- (3) 수막강내 또는 뇌실내 주사
(1 mL중 100 mg이 함유된 이 약의 주사제는 고장액이므로 수막강투여에 적합하지 않다.)

3) 투여부위

- (1) 정맥투여 : 가능한 한 주입용 튜브를 통해 2~3분 이상 투여한다.
- (2) 100 mg 초과량 투여 시는 통상 정맥주입으로 하여 24시간 이내에서 실시한다(최초 투여 시 급속투여로 한다).
- (3) 70 mg/m²(체중 kg당 2.3 mg) 초과량은 로이코보린 구원요법과 병행하거나 투여 후 24~48시간의 혈청메토포레이트치에 대한 분석을 실시해야 한다.

13. 보관 및 취급상의 주의사항

- 1) 소아의 손이 닿지 않는 곳에 보관한다.
- 2) 다른 용기에 넣는 것은 사고원인이 되거나 품질유지 면에서 바람직하지 않으므로 주의한다.

■ 저장방법

밀봉용기, 25℃이하 차광보관

■ 포장단위

50mg / 2ml × 5 바이알
500mg/20ml × 1 바이알
1g/10ml × 1 바이알
5g/50ml × 1 바이알

■ 제 조 원

호스피라사, 오스트레일리아
(Hospira Australia Pty Ltd,
1 Lexia Place, Mulgrave, Victoria 3170, Australia)

※사용기한이 경과되었거나 변질·변패·오손된 제품을 구입하였을 때에는 구입한 약국, 도매상, 병·의원을 통하여 즉시 교환해 드립니다.

작성일자 : 2011. 2. 1



수입·판매원

호스피라코리아 (주)

서울시 강남구 삼성동 159-6번지 도심공향 6층 616호

Tel. 02)209-4800

www.hospira.co.kr

25INS000047KR

WARNING

- Methotrexate must only be used by physicians experienced in anti-metabolite chemotherapy, or in the case of non-oncological conditions, by a specialist physician.
- Patients should be fully informed of the risk of fatal or severe toxic reactions involved with the administration of methotrexate and should be under constant supervision of the physician.
- Deaths have been reported with the use of methotrexate. In the treatment of psoriasis and rheumatoid arthritis, methotrexate should be restricted to severe, recalcitrant, disabling disease which is not adequately responsive to other forms of therapy and only when the diagnosis has been established, by biopsy and/or after consultation.
- Methotrexate may produce depression of the bone marrow, anaemia, aplastic anaemia, leucopenia, neutropenia, thrombocytopenia and bleeding.
 - At high or prolonged doses, methotrexate may be hepatotoxic. Liver atrophy, necrosis, cirrhosis, fatty changes and periportal fibrosis have been reported. Since changes may occur without previous signs of gastro-intestinal or haematological toxicity, it is imperative that hepatic function be determined prior to initiation of treatment and monitored regularly throughout therapy. Special caution is indicated in the presence of liver damage or impaired hepatic function. Concomitant use of other drugs with hepatotoxic potential and alcohol should be avoided.
 - Malignant lymphomas, which may regress following withdrawal of methotrexate, may occur in patients receiving low-dose methotrexate and, thus, may not require cytotoxic treatment. Discontinue methotrexate first and, if the lymphoma does not regress, appropriate treatment should be instituted.
 - Potentially fatal opportunistic infections, especially *Pneumocystis carinii* pneumonia, may occur with methotrexate therapy.
 - Use in pregnancy**
Category D. This category specifies drugs, which have caused an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.

Methotrexate has caused foetal death and/or congenital anomalies. It should not be used in pregnant women or in those who might become pregnant unless the potential benefits can be expected to outweigh the considered risks. Methotrexate is contraindicated in the treatment of psoriasis and rheumatoid arthritis in pregnant women. Women of childbearing potential should not be started on methotrexate until pregnancy is excluded and should be fully counselled on the serious risk to the foetus should they become pregnant while undergoing treatment.

Pregnancy should be avoided if either partner is receiving methotrexate, during and for a minimum of 3 months after therapy has ceased, although the optimal time interval between the cessation of methotrexate treatment of either partner, and pregnancy, has not been clearly established.
 - Methotrexate is usually contraindicated in patients with impaired renal function.
 - Serious adverse effects including marrow suppression, aplastic anaemia, gastrointestinal toxicity and death have been reported with concomitant administration of methotrexate (usually in high doses) with nonsteroidal anti-inflammatory drugs (NSAIDs).
 - Diarrhoea and ulcerative stomatitis are frequent toxic effects and require interruption of therapy, otherwise haemorrhagic enteritis and death from intestinal perforation may occur.
 - Pulmonary toxicity including acute or chronic interstitial pneumonitis and pulmonary fibrosis, which can progress rapidly and is potentially fatal, has been associated with methotrexate therapy. It may occur acutely at any time during therapy and has been reported at low doses. Methotrexate should be discontinued and careful clinical evaluation be performed in patients developing symptoms of pulmonary toxicity (eg. Dry, non-productive cough, dyspnoea). Management of methotrexate-induced pulmonary toxicity is mainly supportive. Methotrexate-induced pulmonary toxicity may not be fully reversible. Pulmonary lesions can occur at all dosages. Infection (including pneumonia) needs to be excluded. Patients should be closely monitored for pulmonary symptoms.
 - Methotrexate has been used in high-dosage schedules followed by calcium folinate (leucovorin calcium) in the adjuvant treatment of certain neoplastic diseases. This procedure is complicated and hazardous. It should not be attempted except by highly experienced teams following carefully designed protocols. The recent published literature should always be consulted.
 - Use in children**
Aside from its established use in cancer chemotherapy; the safety and efficacy of using methotrexate in children has not been fully elucidated.
 - Only preservative-free methotrexate should be used for intrathecal administration.
 - Both the physician and the pharmacist should emphasise to the patient the importance of the weekly dosing regimen: mistaken daily use may cause serious and sometimes life-threatening or fatal toxicity. For the same reason great care should be taken with dispensing to ensure the correct tablet strength of methotrexate is given to the patient.
 - Methotrexate given concomitantly with radiotherapy may increase the risk of soft tissue necrosis and osteonecrosis.

Name of the Medicine

Methotrexate BP

Description

DBL® Methotrexate Injection is a sterile solution of Methotrexate BP in Water for Injections BP. Sodium chloride is included for isotonicity except in the 1 g/10 mL vial. DBL® Methotrexate Injection is preservative-free. DBL® Methotrexate Injection has a pH of 7.5 to 9.0. DBL® Methotrexate Tablets contain 2.5 mg of Methotrexate BP. The 2.5 mg tablets are unscored.

Pharmacology

Methotrexate is an antimetabolite antineoplastic agent, which exerts its cytotoxic effect through competitive inhibition of dihydrofolate reductase, the enzyme that reduces folic acid to tetrahydrofolic acid. Inhibition of tetrahydrofolic acid results in interference with DNA synthesis and cellular reproduction.

Tissues with high rates of cellular proliferation, eg. malignant cells, bone marrow, foetal cells, dermal epithelium, buccal and intestinal mucosa and cells of the urinary bladder are generally more sensitive to this effect of methotrexate.

In psoriasis, the rate of production of epithelial cells in the skin is greatly increased over normal skin. This differential in reproductive rates provides the basis for use of methotrexate to control the psoriatic process.

In patients with rheumatoid arthritis, effects of methotrexate on articular swelling and tenderness can be seen as early as three to six weeks. Although methotrexate clearly ameliorates symptoms of inflammation (pain, swelling, stiffness) there is no evidence that it reduces remission of rheumatoid arthritis nor has a beneficial effect been demonstrated on bone erosion and other radiological changes which result in impaired joint use, functional disability and deformity. Most studies of methotrexate in patients with rheumatoid arthritis are relatively short term (three to six months). Data from long-term studies indicate that an initial clinical improvement is maintained for at least two years with continued therapy.

Pharmacokinetics

Methotrexate at low doses (<25 mg/m²) is well absorbed from the gastrointestinal tract; at larger doses absorption may become erratic and incomplete. Peak serum levels may be achieved within 1 to 4 hours following oral administration, and within 0.5 to 2 hours following intravenous (IV) or intramuscular (IM) administration.

Approximately 50% of the absorbed methotrexate is reversibly bound to serum proteins. Methotrexate is widely distributed into body tissues and concentrates in the kidneys, liver and gastrointestinal tract. It also distributes into third-space accumulation of fluid, eg. ascites or pleural effusions. Methotrexate does not reach therapeutic concentrations in the cerebrospinal fluid (CSF) when given orally or parenterally. High concentrations of the drug, when needed, may be attained by intrathecal injection.

Methotrexate does not appear to be appreciably metabolised. Methotrexate is predominantly excreted by the kidneys and small amounts appear in the faeces. Excretion of methotrexate is reduced in the presence of impaired renal function.

Indications

Antineoplastic chemotherapy

Methotrexate has a broad spectrum of antineoplastic activity. It is indicated for the treatment of breast cancer, gestational choriocarcinoma, and in patients with choriadenoma destruens and hydatidiform mole.

Methotrexate may be used in combination with other chemotherapeutic agents for the palliative treatment of acute leukaemias, particularly acute lymphoblastic leukaemia. It may also be used in the treatment of Burkitt's lymphoma, advanced stages (III and IV, Peters' Staging System) of lymphosarcoma, especially in children, and in advanced cases of mycosis fungoides.

High dose therapy

In high-dose schedules, methotrexate may be effective alone or in combination therapy, in the treatment of epidermoid cancers of the head and neck, osteogenic sarcoma and bronchogenic carcinoma.

Calcium folinate (leucovorin calcium) must be used in conjunction with high dose methotrexate therapy.

Psoriasis chemotherapy (see WARNING box)

Methotrexate may be of value in the symptomatic control of severe, recalcitrant, disabling psoriasis which is not adequately responsive to other forms of treatment. However, due to the high risk associated with its use, methotrexate should be used after the diagnosis has been definitely established, as by biopsy and/or after dermatologic consultation.

Rheumatoid arthritis chemotherapy (see WARNING box)

Management of severe, recalcitrant, active rheumatoid arthritis in adults not responding to, or intolerant of, an adequate trial of NSAIDs and one or more disease modifying drugs.

Aspirin, NSAIDs and/or low dose steroids may be continued, although the possibility of increased toxicity with concomitant use of NSAIDs including salicylate has not been fully explored.

Steroids may be reduced gradually in patients who respond to methotrexate.

Combined use of methotrexate with gold, penicillamine, hydroxychloroquine, sulfasalazine or cytotoxic agents has not been studied and may increase the incidence of adverse effects. Rest and physiotherapy as indicated should be continued.

Contraindications

Methotrexate is contraindicated in patients with severe renal impairment.

In the treatment of psoriasis and rheumatoid arthritis, methotrexate is contraindicated in pregnant women and in patients with poor nutritional status, bone marrow depression, hepatic disorders or in those with pre-existing blood dyscrasias such as bone marrow hypoplasia, leucopenia, thrombocytopenia or anaemia.

Methotrexate is contraindicated in patients with overt or laboratory evidence of immunodeficiency syndrome(s).

Breast feeding is contraindicated in women taking methotrexate.

Methotrexate is contraindicated in rheumatoid arthritis patients with active, infectious disease or psoriasis patients with serious infections, and in psoriasis and rheumatoid arthritis patients with peptic ulcer disease or ulcerative colitis. Methotrexate is contraindicated in psoriatic and rheumatoid arthritis patients suffering severe renal disorders, alcoholism or hepatic disorders including alcoholic liver disease or other chronic liver disease.

Methotrexate is contraindicated in patients with a known hypersensitivity to it or to any of the excipients.

Radiotherapy to the central nervous system should not be given concurrently with intrathecal methotrexate.

An increased risk of hepatitis has been reported to result from combined use of methotrexate and etretinate. Therefore, the combination of methotrexate and acitretin is also contraindicated.

Precautions (see WARNING box)

Methotrexate must only be used by physicians experienced in antimetabolite chemotherapy or, in the case of non-oncological conditions, by a specialist physician.

Methotrexate has a high potential for toxicity, which is usually dose-related. The physician should be familiar with the various characteristics of the drug and its established clinical usage. Because the toxic effects can occur at any time during methotrexate therapy, patients **must** be kept under appropriate supervision so that signs or symptoms of possible toxicity or adverse effects may be detected as early as possible. This is especially important in patients undergoing high dose therapy or in those where drug elimination could be impaired (renal impairment, pleural effusion, ascites). When such reactions do occur, the drug should be reduced in dosage or discontinued and appropriate corrective measures should be taken. If methotrexate therapy is reinstituted, it should be carried out with utmost caution, with adequate consideration of further need for the drug, and with increased alertness as to possible recurrence of toxicity.

Pretreatment and periodic haematologic evaluations are essential to the use of methotrexate in chemotherapy because of its haematopoietic suppressive effects, manifesting as anaemia, aplastic anaemia, pancytopenia, leucopenia, neutropenia and/or thrombocytopenia. This may occur abruptly and on apparent safe dosage, and any profound drop in blood-cell count indicates immediate cessation of the drug and appropriate therapy. Methotrexate should be used with caution, if at all, in patients with malignant disease who have pre-existing bone marrow aplasia, leucopenia, thrombocytopenia, or anaemia.

Check the following before and during use

As methotrexate is excreted primarily by the kidney, its use in the presence of impaired renal function may lead to drug accumulation with resultant toxicity or even additional renal damage. The renal status of the patient should be determined prior to and periodically during methotrexate therapy. Caution should be exercised if significant renal impairment is present. Drug dosage should be reduced or discontinued until renal function is improved or restored. The urine should be kept alkaline throughout therapy with methotrexate (methotrexate is a weak acid and tends to precipitate at urine pH below 6.0)

Methotrexate may cause renal damage that may lead to acute renal failure. Close attention to renal function including adequate hydration, urine alkalisation, and measurement of serum methotrexate and renal function are recommended.

If vomiting, diarrhoea or stomatitis occur, resulting in dehydration, methotrexate should be discontinued until recovery occurs.

Care should be exercised whenever packed red blood cells and methotrexate are given concurrently. Patients receiving 24 hour methotrexate infusion and subsequent transfusions have showed enhanced toxicity probably resulting from prolonged serum methotrexate concentrations.

Methotrexate is an immunosuppressant and may reduce immunological response to concurrent vaccination. Severe antigenic reactions may occur if a live vaccine is given concurrently.

Incompatibilities

Methotrexate has been reported to be incompatible with cytarabine, fluorouracil and prednisolone.

Instructions to patients

1. Patients should be informed of the potential benefit and risk in the use of methotrexate. The risk of effects on reproduction should be discussed with both male and female patients taking methotrexate.
2. Patients should be informed of the early signs and symptoms of toxicity, of the need to see their doctor promptly if they occur, and the need for close follow-up, including periodic laboratory tests to monitor toxicity.
3. Patients receiving methotrexate should avoid excessive unprotected exposure to sun or sunlamps because of possible photosensitivity reactions.
4. Adverse reactions to methotrexate, such as dizziness and fatigue may affect the ability to drive or operate machinery.

Adverse Effects

The major toxic effects of methotrexate occur on normal, rapidly proliferating tissues, particularly the bone marrow and gastrointestinal tract. Ulcerations of the oral mucosa are usually the earliest signs of toxicity.

Ulcerative stomatitis, leucopenia, nausea and abdominal distress are the most common adverse effects. Others reported include malaise, undue fatigue, chills and fever, dizziness, drowsiness, tinnitus, blurred vision, eye discomfort and decreased resistance to infection. The incidence and severity of side effects generally appear to be dose- and frequency-related. Adverse effects have been reported for the various systems:

Skin: dermatitis, erythematous rashes, pruritis, urticaria, photosensitivity, depigmentation/ hyperpigmentation, alopecia, vasculitis, petechiae, ecchymosis, telangiectasia, acne, folliculitis, furunculosis, nail changes. Burning and erythema may appear in psoriatic areas for 1 to 2 days following each dose. Rarely, painful plaque erosions may appear. Lesions of psoriasis may be aggravated by concomitant exposure to ultraviolet radiation. Skin ulceration has been reported in psoriatic patients. Anaphylactic reactions and skin ulceration/necrosis consistent with toxic epidermal necrolysis, soft tissue necrosis and osteonecrosis have also been reported. Severe, occasionally fatal, dermatologic reactions, including toxic epidermal necrolysis, Stevens-Johnson syndrome, exfoliative dermatitis, skin necrosis, and erythema multiforme have been reported in children and adults within days of oral, intramuscular, intravenous or intrathecal methotrexate administration. Reactions were noted after single or multiple low, intermediate or high doses of methotrexate in patients with neoplastic and non-neoplastic diseases.

Blood and lymphatic system: bone marrow depression, leucopenia, neutropenia, eosinophilia, pancytopenia, agranulocytosis, thrombocytopenia, anaemia (including aplastic anaemia), hypogammaglobulinaemia, decrease in serum albumin. Clinical sequelae such as fever, infections, haemorrhage from various sites, septicæmia, lymphadenopathy and proliferative disorders may be expected. Megaloblastic anaemia has also been reported, mainly in elderly patients receiving long-term methotrexate therapy. Folate supplementation may permit continuation of methotrexate therapy with resolution of anaemia.

Cardiovascular system: Pericarditis, vasculitis, pericardial effusion, hypotension and thromboembolic events (including arterial thrombosis, cerebral thrombosis, deep vein thrombosis, retinal vein thrombosis, thrombophlebitis and pulmonary embolus) have been reported with methotrexate therapy.

Alimentary system: mucositis (gingivitis, pharyngitis, stomatitis, glossitis), anorexia, nausea, vomiting, diarrhoea, abdominal distress, hæmatemesis, melenia, gastrointestinal ulceration and bleeding, intestinal perforation, pancreatitis, enteritis, acute and chronic hepatic toxicity resulting in acute liver atrophy, necrosis, fatty metamorphosis, acute hepatitis, periportal fibrosis, or hepatic cirrhosis, elevated liver enzymes, decreased serum albumin and hepatic failure. In rare cases, the effect of methotrexate on the intestinal mucosa has led to malabsorption or toxic megacolon. Alteration of liver function tests (increases in transaminases and LDH levels) is commonly reported but usually resolves within one month of cessation of therapy.

Urogenital system: renal failure, dysuria, azotaemia, cystitis, haematuria, defective oogenesis or spermatogenesis, transient oligospermia, urogenital or menstrual dysfunction, infertility, abortion, foetal defects, foetal death, severe nephropathy, vaginitis, vaginal discharge.

Pulmonary system: interstitial pneumonitis, interstitial fibrosis, reversible eosinophilic pulmonary infiltrates, respiratory fibrosis, respiratory failure, chronic interstitial obstructive pulmonary disease, alveolitis, death. Manifestations of methotrexate-induced pulmonary toxicity commonly include fever, cough (especially dry and non-productive), dyspnoea, chest pain, hypoxaemia and/or radiological evidence of pulmonary infiltrates (usually diffuse and/or alveolar).

Central nervous system: headaches, drowsiness, blurred vision, speech impairment including dysarthria and aphasia, and coma. Aphasia, hemiparesis and convulsions have occurred possibly related to haemorrhage or to complications from intra-arterial catheterization. Convulsion, paresis, Guillain-Barre syndrome and increased cerebrospinal fluid pressures have followed intrathecal administration. Following low doses, occasional patients have reported transient subtle cognitive dysfunction, mood alteration or unusual cranial sensations. Cognitive impairment has been recorded in children who received intrathecal methotrexate together with cranial irradiation. There have been reports of leucoencephalopathy following IV administration of methotrexate in high doses to patients who have had craniospinal irradiation. Serious neurotoxicity, frequently manifested as generalised or focal seizures, has been reported with unexpectedly increased frequency among paediatric patients with acute lymphoblastic leukaemia who were treated with intermediate-dose intravenous methotrexate (1 gram/m²). Symptomatic patients were commonly noted to have leucoencephalopathy, encephalopathy and/or microangiopathic calcifications on diagnostic imaging studies.

After the intrathecal or high dose use of methotrexate, the central nervous system toxicity which may occur can be classified as follows:

1. chemical arachnoiditis manifested by such symptoms as headache, back pain, nuchal rigidity and fever;
2. paresis, usually transient, manifested by paraplegia and increased CSF pressure associated with involvement with one or more spinal nerve roots;
3. a delayed syndrome occurring months to years after treatment characterised by necrotising leucoencephalopathy and manifested by confusion, irritability, somnolence, ataxia, dementia, occasionally convulsions and, rarely, death. The effects are dose-related and occur particularly when intrathecal methotrexate is given at doses greater than 50 mg in combination with cranial irradiation and systemic methotrexate therapy.

Ophthalmic: conjunctivitis, eye discomfort, blurred vision and serious visual changes of unknown aetiology including transient blindness have been reported in patients receiving methotrexate.

Infections: There have been case reports of sometimes fatal opportunistic infections in patients receiving methotrexate therapy for neoplastic and non-neoplastic diseases. *Pneumocystis carinii* pneumonia was the most common infection. Other reported infections include pneumonia, sepsis, nocardiosis, histoplasmosis, cryptococcosis, *Herpes Zoster*, *H.simplex* hepatitis, disseminated *H.simplex*, fatal sepsis and cytomegalovirus, including cytomegaloviral pneumonia.

Carcinogenicity: Cytotoxic drugs have been reported to be associated with an increased risk of development of secondary tumours in humans. Evidence of chromosomal damage to animal somatic cells and human bone marrow cells has been reported with methotrexate. Reports of lymphoma, including reversible lymphomas and tumour lysis syndrome have been documented in patients treated with methotrexate.

Other reactions related to or attributed to the use of methotrexate, such as metabolic changes, precipitation of diabetes, osteoporotic effects (including aseptic necrosis of the femoral head), abnormal changes in tissue cells, arthralgia/myalgia, proteinuria, nodulosis, stress fractures, loss of libido, impotence and even sudden death, have been reported.

Radiation dermatitis and sunburn may be "recalled". A few cases of anaphylactoid reactions have been reported.

Dosage and Administration

Because of its potential to cause severe toxicity, methotrexate therapy requires close supervision with particular caution to distinguish between daily and weekly dosage regimens. Weekly dosage prescriptions should specify a particular day of the week.

(a) Antineoplastic chemotherapy

Oral administration of methotrexate in tablet form is often preferred since absorption is rapid and effective serum levels are obtained. It is recommended that oral methotrexate should be taken on an empty stomach.

Methotrexate may be administered by intramuscular, intravenous, intra-arterial or intrathecal injection. Non-isotonic solutions of DBL® Methotrexate Injection should not be administered intrathecally.

A guideline of a ratio of 1:30 is given for the conversion of mg/kg body weight to mg/m² body surface area. The conversion factor varies between 1:20 and 1:40 depending on age and body build.

Trophoblastic neoplasms

The usual dosage is 15 to 30 mg daily orally or IM for 5 days. A repeat course may be given after a period of one or more weeks provided all signs of toxicity have disappeared. Three to five courses of therapy are usually employed. The effectiveness of therapy is ordinarily evaluated by 24 hour quantitative analysis of urinary chorionic gonadotrophin hormone (CGH) which should return to normal or less than 50 IU/24 hours, usually after the 3rd or 4th course. Complete resolution of measurable lesions usually occur 4 to 6 weeks later. One to two courses of methotrexate after normalization of CGH are usually recommended. Before each course of methotrexate, careful clinical assessment is essential. Cyclic combination therapy of methotrexate with other antineoplastic drugs has been reported as being useful.

Since hydatidiform mole may precede choriocarcinoma, prophylactic chemotherapy with methotrexate has been recommended. Chorioadenoma destruens is considered to be an invasive form of hydatidiform mole. Methotrexate is administered in these disease states in doses similar to those recommended for trophoblastic neoplasms.

Breast carcinoma

Prolonged cyclic combination chemotherapy with cyclophosphamide, methotrexate and fluorouracil has given good results when used as adjuvant treatment to radical mastectomy in primary breast cancer with positive axillary lymph nodes. Methotrexate dosage was 40 mg/m² intravenously on the first and eighth days.

Leukaemia

Acute lymphatic (lymphoblastic) leukaemia in children and young adolescents is the most responsive to present day chemotherapy. In young adults and older patients, clinical remission is more difficult to obtain and early relapse is more common. In chronic lymphatic leukaemia, the prognosis for adequate response is less encouraging.

Methotrexate in doses of 3.3 mg/m² orally in combination with prednisolone 60 mg/m² daily has been given for induction of remission of lymphoblastic leukaemia. When remission and general clinical improvement have been attained, a maintenance dosage of methotrexate 30 mg/m² orally or IM twice weekly may be given. This treatment is expected to produce remission in 50% of patients treated, usually within 4 to 6 weeks.

Alternatively, 2.5 mg/kg IV every 14 days may be given. Should relapse occur, reinduction of remission can again usually be obtained by repeating the initial induction regimen. A variety of dosage schedules for both induction and maintenance of remission with various combinations of alkylating and antifolic agents have recently been introduced. Multiple drug therapy with several agents, including methotrexate given concomitantly, appears to be gaining increasing support in both the acute and chronic forms of leukaemia.

Acute granulocytic leukaemia is rare in children but common in adults. This form of leukaemia responds poorly to chemotherapy and remissions are short with relapses common. Resistance to therapy also develops rapidly.

Meningeal leukaemia

Patients with leukaemia are subject to leukaemic invasion of the central nervous system. This may manifest characteristic signs or symptoms or remain silent and be diagnosed only by examination of the cerebrospinal fluid (CSF), which contains leukaemic cells in such cases. Therefore, the CSF should be examined in all leukaemic patients. Since passage of methotrexate from blood serum to the CSF is minimal, for adequate therapy the drug is administered intrathecally. Only preservative-free methotrexate should be used for intrathecal administration.

It is now common practice to administer methotrexate intrathecally as prophylaxis in all cases of acute lymphocytic leukaemia.

By intrathecal injection the distribution of methotrexate is in the CSF, the volume of which is dependent upon age and not body surface area. The CSF is at 40% of adult volume at birth and reaches adult volume in several years. The recommended dose by age is:

Age (yrs)	less than 1	1	2	3+ older
Dose (mg)	6	8	10	12

There is some indication that infants less than 4 months and adults 70 years of age or older may have increased acute toxicity with the doses recommended and dose reduction may be indicated.

For the treatment of meningeal leukaemia, intrathecal methotrexate may be given at intervals of 2 to 5 days, however there is some indication that doses given at intervals of less than one week may result in increased toxicity.

Methotrexate is administered until the cell count of the cerebrospinal fluid returns to normal, then one additional dose of the drug is administered.

For prophylaxis against meningeal leukaemia, the dosage is the same as for treatment except for the intervals of administration. On this subject, it is advisable for the physician to consult the medical literature.

Large doses may cause convulsions. Untoward side effects may occur with any given intrathecal injection and are commonly neurological in character.

Methotrexate given by the intrathecal route appears in significant concentrations in the systemic circulation and may cause systemic methotrexate toxicity. Therefore systemic antileukaemic therapy with the drug should be appropriately adjusted, reduced or discontinued. Focal leukaemic involvement of the central nervous system may not respond to intrathecal chemotherapy and is best treated with radiotherapy.

Lymphomas

The usual dosage of methotrexate for the treatment of stage I or II of Burkitt's lymphoma is 10 to 25 mg per day orally for 4 to 8 days. In stage III methotrexate is commonly given concomitantly with other antineoplastic agents. In all stages, several courses of drug therapy are usually administered interspersed with 7 to 10 day rest periods. Lymphosarcomas in stage III may respond to combined drug therapy with methotrexate given in doses of 0.625 mg to 2.5 mg/kg daily.

Methotrexate is of no value in the treatment of Hodgkin's Disease.

Mycosis fungoides

Dosage of methotrexate for the treatment of mycosis fungoides is usually 2.5 to 10 mg orally each day for weeks or months. Initial dosage and dosage adjustment are determined by patient response and haematologic monitoring.

Methotrexate has also been given IM in doses of 50 mg once weekly or 25 mg twice weekly.

Methotrexate appears to produce clinical remissions in 50% of the cases treated.

Methotrexate has been associated with pulmonary toxicity, which is potentially fatal. Patients should be closely monitored for pulmonary symptoms. Methotrexate should be discontinued and careful clinical evaluation should be performed in patients developing pulmonary manifestations (especially a dry, non-productive cough). Although clinically variable, the typical patient with methotrexate-induced lung disease presents with fever, cough, chest pain, dyspnoea, hypoxaemia and an infiltrate on X-ray; infection needs to be excluded. This lesion can occur at all dosages (see **WARNING** box). Infection (including pneumonia) needs to be excluded.

The following laboratory tests should be carried out as part of the essential clinical evaluation and appropriate monitoring of patients on methotrexate therapy; complete haemogram; haematocrit; urinalysis; renal and liver function tests. A chest x-ray is recommended. The tests should be performed prior to, during and after therapy. During therapy for psoriasis, monitoring of the following parameters is recommended: haematology at least monthly, liver and renal function every one to three months. More frequent monitoring is usually indicated during antineoplastic therapy. It is important to perform liver biopsy or bone marrow aspiration studies where high dose or long term therapy is being followed. Pulmonary function tests may be useful if methotrexate-induced lung disease is suspected, especially if baseline measurements are available.

During therapy of rheumatoid arthritis and psoriasis, monitoring of the following parameters is recommended: haematology at least monthly, hepatic enzyme levels and renal function every 1 to 2 months. More frequent monitoring is usually indicated during antineoplastic therapy. During initial or change in dosing, or during periods of increased risk of elevated methotrexate blood levels (eg. dehydration), more frequent monitoring may also be indicated.

Methotrexate should be used with extreme caution in the presence of infection, peptic ulcer, ulcerative colitis, debility, and in extreme youth and old age.

Methotrexate should be used with extreme caution in the presence of active infection, and is usually contraindicated in patients with overt or laboratory evidence of immunodeficiency syndromes.

Like other cytotoxic drugs, methotrexate may induce "tumour lysis syndrome" in patients with rapidly growing tumours. Appropriate supportive and pharmacologic measures may prevent or alleviate this complication.

Methotrexate exits slowly from the three-space compartments (eg pleural effusions or ascites). This results in a prolonged terminal phase half life and unexpected toxicity. In patients with significant three-space accumulation, it is advisable to evacuate the fluid before treatment and to monitor plasma methotrexate levels.

Methotrexate causes hepatotoxicity, liver fibrosis and cirrhosis, but generally only after prolonged use. Liver enzyme elevations are frequently seen. These are usually transient and asymptomatic and do not appear predictive of subsequent hepatic disease. Liver biopsy after sustained use often shows histological changes, and fibrosis and cirrhosis have been reported; these latter lesions may not be preceded by symptoms or abnormal liver function tests in the psoriasis population. Periodic liver biopsies are usually recommended for psoriatic patients who are under long-term treatment. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in the rheumatoid arthritis population.

The risk of developing acute hepatitis and chronic hepatotoxicity in psoriatic patients seems to be correlated not only to the cumulative dose of methotrexate but also to the presence of concurrent conditions such as alcoholism, obesity, diabetes, advanced age and arsenical compounds. Chronic toxicity is potentially fatal; it generally has occurred after prolonged use (generally 2 years or more) and after a total cumulative dose of at least 1.5 grams.

In psoriasis, liver damage and function tests, including serum albumin and prothrombin time, should be performed several times prior to dosing. Liver function tests are often normal in developing fibrosis or cirrhosis. These lesions may be detectable only by biopsy. It is recommended to obtain a liver biopsy at: 1) before start of therapy or shortly after initiation of therapy (2 – 4 months); 2) after a total cumulative dose of 1.5 grams; and 3) after each additional 1.0 to 1.5 grams. In case of moderate fibrosis or any cirrhosis, discontinue the drug; mild fibrosis normally suggests a repeat biopsy in 6 months. Milder histologic findings such as fatty change and low grade portal inflammation are relatively common before the start of therapy. Although these mild changes are usually not a reason to avoid or discontinue methotrexate therapy, methotrexate should be used with caution.

In rheumatoid arthritis, age at first use of methotrexate and duration of therapy has been reported as risk factors for hepatotoxicity. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in the rheumatoid population. Liver function tests should be performed at baseline and at 4 – 8 week intervals in patients receiving methotrexate for rheumatoid arthritis. Pretreatment liver biopsy should be performed for patients with a history of excessive alcohol consumption, persistently abnormal alkaline liver function test values, or chronic hepatitis B or C infection. During therapy, liver biopsy should be performed if there are persistent liver function test abnormalities, or there is a decrease in serum albumin below the normal range (in the setting of well controlled rheumatoid arthritis).

If the results of a liver biopsy show mild changes (Roenigk grades I, II, IIIa), methotrexate may be continued and the patient monitored according to the recommendations listed above. Methotrexate should be discontinued in any patient who displays persistently abnormal liver function tests and refuses liver biopsy, or in any patient whose liver biopsy shows moderate to severe changes (Roenigk grade IIIb or IV).

Methotrexate therapy has immunosuppressive activity, which can potentially lead to serious or even fatal infections. Bacterial infection may occur or be a threat if profound leucopenia occurs during therapy. In this instance, the drug should be discontinued and appropriate antibiotic therapy instituted. If severe bone marrow depression occurs, blood or platelet transfusions may be required.

Pneumonia (in some cases leading to respiratory failure) may occur. Potentially fatal opportunistic infections, especially *Pneumocystis carinii* pneumonia, may occur with methotrexate therapy. When a patient presents with pulmonary symptoms, the possibility of *Pneumocystis carinii* pneumonia should be considered.

Immunisation may be ineffective when given during methotrexate therapy. Immunisation with live virus vaccines is generally not recommended. There have been reports of disseminated vaccinia infections after smallpox immunisation in patients receiving methotrexate therapy (see **Drug Interactions**).

Severe, occasionally fatal, skin reactions have been reported following single or multiple doses of methotrexate. Reactions have occurred within days of oral, intramuscular, intravenous, or intrathecal administration. Recovery has been reported with discontinuation of therapy.

When considering the use of methotrexate for chemotherapy, clinicians must evaluate the need and potential value of the drug against the risks, adverse effects or toxic effects. Most adverse effects are reversible if detected early. When such reactions do occur, the dosage should be reduced or drug discontinued and appropriate corrective measures taken. If necessary, this could include the use of leucovorin calcium and/or acute, intermittent haemodialysis with a high-flux dialyser. Caution should be exercised when reinstituting methotrexate therapy and adequate consideration given to the need for further drug administration and alertness to the possible recurrence of toxicity.

High dose therapy

Methotrexate has been used in very high dosage followed by leucovorin rescue in the experimental treatment of certain neoplastic disease. This procedure is investigational and hazardous. It should not be attempted outside of facilities where the necessary expertise and resources have been assembled. The recent published literature should be consulted. Large doses should not be used in patients with impaired renal function or a third-space reservoir such as ascites or large pleural effusion. Renal function and serum levels should be carefully monitored in order to reveal potential toxicity. Administration of calcium folinate is mandatory in high-dose methotrexate therapy. The administration of calcium folinate, hydration and alkalinisation of the urine should be carried out with constant monitoring of the toxic effects and the elimination of methotrexate in order to prevent renal precipitation in acidic urine.

Transient abnormalities of liver function tests (elevated transaminases) are observed frequently but persistent abnormalities and/or significant decreases in serum albumin may indicate serious liver toxicity and require evaluation. Liver biopsy is currently believed to be the only reliable measure of methotrexate-induced hepatotoxicity.

When to perform a liver biopsy in rheumatoid arthritis patients has not been established, either in terms of cumulative methotrexate dose or duration of therapy. There is a combined reported experience in 217 patients with rheumatoid arthritis with liver biopsy both before and during treatment (after a cumulative dose of at least 1500 mg) and in 714 patients with a biopsy only during treatment. There were 64 (7%) cases of fibrosis and only one (0.1%) case of cirrhosis. Of the 64 cases of fibrosis, 60 were deemed mild. The reticulin stain is more sensitive for early fibrosis and its use may increase these figures. It is unknown whether even longer use will increase these risks. When methotrexate is discontinued, a "flare" of arthritis usually occurs within three to six weeks.

Systemic high doses or intrathecal administration of methotrexate may cause significant CNS toxicity. Patients should be closely monitored for neurologic symptoms and if these occur treatment should be discontinued and appropriate therapy instituted.

Both the physician and the pharmacist should emphasise to the patient the importance of the weekly dosage regimens; mistaken daily use may cause serious and sometimes life-threatening or fatal toxicity (see **WARNING** box and **Precautions**).

Carcinogenesis, Mutagenesis, impairment of fertility

Methotrexate is considered to be carcinogenic. However, extensive epidemiologic studies are required to determine its carcinogenicity potential. Methotrexate has been reported to cause chromosome damage. Methotrexate may cause defective oogenesis and spermatogenesis. Therefore, in men and women of fertile age, steps should be taken to avoid conception during methotrexate therapy. The risk of genetic abnormalities may persist after discontinuing methotrexate therapy. Thus, it is advised that both men and women avoid intercourse leading to conception for an indefinite period (at least 12 weeks) after discontinuing methotrexate to ensure the re-establishment of normal germinal cells.

Use in pregnancy (Category D)

Methotrexate has caused foetal death and/or congenital abnormalities; therefore, it is not recommended in women of childbearing potential unless there is appropriate medical evidence that the benefits can be expected to outweigh the considered risks. Pregnant psoriatic or rheumatoid arthritis patients should not receive methotrexate. Women of childbearing potential should not be started on methotrexate until pregnancy is excluded and should be fully counselled on the serious risk to the foetus should they become pregnant while undergoing treatment. Pregnancy should be avoided if either partner is receiving methotrexate, during and for at least 12 weeks after cessation of therapy.

Use in lactation

Methotrexate has been detected in human breast milk and is contraindicated during breastfeeding. Women should be advised not to breast feed while being treated with methotrexate.

Use in Elderly

Due to diminished hepatic and renal functions as well as decreased folate states in elderly patients, relatively low doses should be considered and these patients should be closely monitored.

Drug Interactions

As methotrexate is partly bound to serum proteins, its toxicity may be increased as a result of displacement by certain drugs such as salicylates, phenylbutazone, sulphonamides, sulphphonylureas, phenytoin, tetracyclines, chloramphenicol and para-aminobenzoic acid. These drugs, particularly salicylates and sulphonamides, should not be given concurrently until the significance of these findings is established.

Oral antibiotics such as tetracycline, chloramphenicol and nonabsorbable broad-spectrum antibiotics, may decrease intestinal absorption of methotrexate or interfere with the enterohepatic circulation by inhibiting bowel flora and suppressing metabolism of the drug by bacteria.

The excretion of methotrexate from the body can be markedly reduced by the concurrent use of penicillins and sulfonamides. There is a considerable risk of methotrexate toxicity. Use of methotrexate with penicillins and sulfonamides should be carefully monitored.

Hypolipidaemic compounds such as cholestyramine provided preferential binding sites compared to serum proteins when given in combination with methotrexate. This may lead to decreased methotrexate serum levels.

In inflammatory arthritis, such as rheumatoid arthritis, concomitant treatment with folic acid or folic acid may decrease the incidence or severity of adverse effects from methotrexate therapy. It is not known whether these medications may decrease the efficacy of methotrexate in treating arthritis. Because vitamin preparations containing folic acid or folic acid may decrease the effectiveness or alter the responses to methotrexate these should not be given to patients taking methotrexate for conditions other than arthritis, including in the treatment of neoplastic disease.

NSAIDs should not be administered prior to or concomitantly with high doses of methotrexate. NSAIDs elevate and prolong serum methotrexate levels, resulting in deaths from severe haematologic and gastrointestinal toxicity. These unexpectedly severe toxicities have been reported with concomitant administration of methotrexate and aspirin, other salicylates, asapropazone, diclofenac, indomethacin and ketoprofen. Naproxen has been reported not to affect the pharmacokinetics of methotrexate but a fatal interaction has been reported.

Caution should be used when NSAIDs or salicylates are administered concomitantly with lower doses of methotrexate. These drugs have been reported to reduce the tubular secretion of methotrexate in an animal model and may enhance its toxicity.

Despite the potential interactions, studies of methotrexate in patients with rheumatoid arthritis have usually included concurrent use of dosage regimens of NSAIDs, without apparent problems. It should be appreciated, however, that the doses used in rheumatoid arthritis (7.5 to 15 mg/week) are somewhat lower than those used in psoriasis and the larger doses could lead to unexpected toxicity. Therefore, until more is known about the NSAID/methotrexate interaction, it is recommended that methotrexate dosage be carefully controlled during treatment with NSAIDs.

Probenecid may increase the methotrexate plasma half-life and thereby increase blood levels.

A potential interaction may exist between methotrexate and proton pump inhibitors (eg omeprazole, pantoprazole).

Concomitant use of allopurinol with methotrexate may result in an increased incidence of cytotoxic-induced bone marrow depression.

In the treatment of patients with osteosarcoma, caution must be exercised if high-dose methotrexate is administered in combination with a potentially nephrotoxic chemotherapeutic agent, eg, cisplatin.

Methotrexate is often used in combination with other cytotoxic drugs. Additive toxicity may be expected in chemotherapy regimens which combine drugs with similar pharmacologic effects and special monitoring should be performed with regard to bone marrow depression, renal, gastrointestinal and pulmonary toxicity. The dosage of methotrexate should be adjusted if it is used in combination with other chemotherapeutic agents with overlapping toxicities.

Folate deficiency states may increase methotrexate toxicity. Trimethoprim alone and sulfamethoxazole/ trimethoprim have been reported rarely to increase the toxic effects (eg. bone marrow suppression) of methotrexate, probably by decreased tubular secretion and/or an additive antifolate effect. Increased toxic effects (eg. bone marrow suppression) have also been reported in patients receiving methotrexate and pyrimethamine.

Assay for folate: Methotrexate may inhibit the organism used in the assay and interfere with detection of folic acid deficiency.

The use of nitrous oxide anaesthesia potentiates the effect of methotrexate on folate metabolism, yielding severe, unpredictable myelosuppression and stomatitis. This effect can be reduced by the use of calcium folinate.

Amidodanone administration to patients receiving methotrexate treatment for psoriasis has induced ulcerative skin lesions.

An increased risk of hepatotoxicity has been reported when methotrexate and etretinate are given concurrently (see **Contraindications**).

The potential for increased hepatotoxicity when methotrexate is administered with other hepatotoxic agents has not been evaluated. However, hepatotoxicity has been reported in such cases. Therefore, patients receiving concomitant therapy with methotrexate and other potential hepatotoxins (eg leflunomide, azathioprine, retinoids, sulfasalazine) should be closely monitored for possible increased risk of hepatotoxicity. Methotrexate in combination with leflunomide may also increase the risk of pancytopenia.

Methotrexate may decrease the clearance of theophylline; theophylline levels should be monitored when used concurrently with methotrexate.

Methotrexate increases the plasma levels of mercaptopurine. Combination of methotrexate and mercaptopurine may therefore require dose adjustment.

The administration of asparaginase has been reported to antagonise the effects of methotrexate.

Skin cancer has been reported in a few patients with psoriasis or mycosis fungoides (a cutaneous T-cell lymphoma) receiving concomitant treatment with methotrexate plus PUVA therapy (methoxsalen and ultraviolet light).

High-dosage therapy

Recent published literature should be consulted for details; dosage regimens have varied considerably in different studies depending upon the nature and severity of the disease, the experience of the investigator etc. It must be emphasised that high dosages should be only used by qualified specialists and in hospitals where the necessary facilities are available.

In order to prevent precipitation of methotrexate in the renal tubules, the patients should maintain an adequate urine flow by drinking plenty of fluids for 2 days after a high dose injection (greater than 200 mg), and keep the urine alkaline by using sodium bicarbonate continuously for at least 24 hours afterwards.

(b) Psoriasis chemotherapy

The patient should be fully informed of the risks involved and should be under constant supervision of the physician.

Assessment of renal function, liver function and blood elements should be made by history, physical examination and laboratory tests (such as haemogram, urinalysis, serum creatinine, liver function studies and liver biopsy if indicated) before beginning methotrexate, periodically during methotrexate therapy and before reinstituting methotrexate therapy after a rest period. Appropriate steps should be taken to avoid conception for at least 12 weeks following methotrexate therapy.

There are three commonly used general types of dosage schedules:

- (1) weekly oral or parenteral intermittent large doses;
- (2) divided dose intermittent oral schedule over a 36 hour period;
- (3) daily oral with a rest period.

All schedules should be continually tailored to the individual patient. A single test dose of 5 to 10 mg parenterally one week prior to initiation of therapy is recommended to detect any idiosyncratic reaction.

Recommended dose schedules for a 70 kg adult are:

- (1) Weekly single dose schedule: 10 to 25 mg orally, IM or IV per week until adequate response is achieved. Weekly dosage should not exceed 50 mg.
- (2) Divided dose schedule: 2.5 mg orally at 12 hour intervals for three doses or at 8 hour intervals for four doses each week. Weekly dosage should not exceed 30 mg.
- (3) Daily dose schedule: 2.5 mg orally daily for five days followed by a rest period of at least 2 days. Daily dosage should not exceed 6.25 mg.

Dosage in each schedule may be gradually adjusted to achieve optimal clinical response, but not to exceed the maximum stated. After optimal response has been achieved, each dosage schedule should be reduced to the lowest possible dose with the largest possible rest period. Conventional topical therapy should be resumed as soon as possible.

(c) Rheumatoid arthritis chemotherapy

The patient should be fully informed of the risks involved and should be under constant supervision of the doctor.

Assessment of haematological, hepatic, renal and pulmonary function should be made by history, physical examination and laboratory tests before beginning, periodically during and before reinstituting methotrexate therapy. Appropriate steps should be taken in men and women to avoid conception during methotrexate therapy.

Both the doctor and the pharmacist should emphasise to the patient the importance of the weekly dosage regimens: mistaken daily use may cause serious and sometimes life threatening or fatal toxicity.

All schedules should be continually tailored to the individual patient. An initial test dose may be given prior to the regular dosing schedule to detect any extreme sensitivity to adverse effects. Complete blood count with platelets should be evaluated seven to ten days later.

Recommended starting dosage schedules are single oral doses of 7.5 mg once weekly, or divided oral doses of 2.5 mg at twelve hour intervals for three doses given as a course once weekly.

Therapeutic response usually begins within three to six weeks and the patient may continue to improve for another twelve weeks or more. The dosage in each schedule may be increased to 15 mg/week after six weeks in non-responsive patients. If necessary, dosage may be gradually increased further to achieve optimal response, but not ordinarily to exceed a total weekly dosage of 20 mg. Once response has been achieved, each schedule should be reduced, if possible, to the lowest possible amount of drug and with the longest rest period.

The optimal duration of therapy is unknown. Limited data available from long-term studies indicate that the initial clinical improvement is maintained for at least two years with continued therapy. When methotrexate is discontinued, the arthritis usually worsens within three to six weeks.

Instructions for handling:

The following protective recommendations are given due to the toxic nature of this substance:

- personnel should be trained in good handling technique
- pregnant staff should be excluded from working with this drug
- personnel handling injectable methotrexate should wear protective clothing including goggles, gowns and disposable gloves and masks
- a designated area should be assigned for preparation (preferably under a laminar flow system), with the work surface protected by disposable, plastic-backed, absorbent paper
- all items used for administration or cleaning, including gloves, should be placed in high-risk, waste disposal bags for high temperature incineration
- accidental contact with the skin or eyes should be treated immediately by copious lavage with water or sodium bicarbonate solution; medical attention should be sought.

Stability

The liquid vials are preservative-free and should therefore be used once only and discarded.

DBL® Methotrexate Injection , when diluted to a concentration of 1 mg/mL with sodium chloride 0.9% injection, glucose 5% injection, Hartmann's Injection, Ringer's Injection and 5% glucose in 0.9% sodium chloride injection, retains its potency for 24 hours when stored at room temperature in the presence and absence of fluorescent light.

However, because of microbiological contamination hazards, infusion of the admixed solutions should commence as soon as possible after preparation, and in any case, should be completed within 24 hours. Storage of admixed solutions should be at 2 to 8°C.

Caution

Pharmacist: Because of its potential to cause severe toxicity, methotrexate therapy requires close supervision of the patient by the physician. Pharmacists should dispense no more than a seven (7) day supply of the drug at one time. Refill of such prescriptions should be by direct order (written or oral) of the physician only.

Overdosage

Discontinue methotrexate at the first sign of ulceration or bleeding, diarrhoea or marked depression of the haematopoietic system.

Symptoms commonly reported following oral overdose include those symptoms and signs reported at pharmacological doses, particularly haematological and gastrointestinal reactions. For example, leucopenia, thrombocytopenia, anaemia, pancytopenia, bone marrow suppression, mucositis, oral ulceration, nausea, vomiting, gastrointestinal ulceration, gastrointestinal bleeding. In some cases, no symptoms were reported. There have been reports of death following overdose. In these cases, events such as sepsis or septic shock, renal failure, and aplastic anaemia were also reported.

Symptoms following injectable overdose would be expected to produce effects, which are an extension of the pharmacological effects. The toxic reactions expected would include those listed under **Adverse Effects**.

Calcium folinate (leucovorin calcium) is a potent agent for neutralising the immediate toxic effects of methotrexate on the haematopoietic system. In general, when overdose is suspected, the dose of calcium folinate should be equal to or higher than the offending dose of methotrexate, and should be given as soon as possible, preferably within the first hour after which it is much less effective. Calcium folinate may be administered by IV infusion in doses of up to 75 mg within 12 hours, followed by 12 mg IM every 6 hours for 4 doses. When average doses of methotrexate appear to have an adverse effect, 6 to 12 mg of calcium folinate may be given IM every 6 hours for 4 doses.

Concomitant hydration and alkalinisation of the urine with sodium bicarbonate is recommended to prevent precipitation of methotrexate or its metabolite in the renal tubules. Patients undergoing methotrexate therapy should be advised to increase fluid intake. Neither standard haemodialysis nor peritoneal dialysis have been shown to significantly improve methotrexate elimination. Some clearance of methotrexate may be obtained by haemodialysis if the patient is totally anuric and no other therapeutic options are available. Effective clearance of methotrexate has been reported with acute, intermittent haemodialysis using a high-flux dialyzer.

Patients who experience delayed early methotrexate elimination are likely to develop non reversible oliguric renal failure. In addition to appropriate leucovorin therapy, these patients require continuing hydration and urinary alkalinisation, and close monitoring of fluid and electrolyte status, until the serum methotrexate level has fallen to below 0.05 micromolar and the renal failure has resolved. If necessary, acute, intermittent haemodialysis with a high-flux dialyzer may also be beneficial in these patients.

In case of overdose, immediately contact the Poisons Information Centre for advice. (In Australia, call 13 11 26; in New Zealand call 0800 764 766.)

Storage

DBL® Methotrexate Injection should be stored below 25°C and protected from light.

DBL® Methotrexate Tablets should be stored below 30°C.

Presentation

DBL® Methotrexate Injection:

- DBL® Methotrexate Injection 5 mg/2 mL vials
- DBL® Methotrexate Injection 50 mg/2 mL vials
- DBL® Methotrexate Injection 500 mg/20 mL vials
- DBL® Methotrexate Injection 1 g/10 mL vials

Methotrexate Tablets:

DBL® Methotrexate Tablets 2.5 mg 30 tablets

Name and Address of Sponsor

Australian Sponsor
Hospira Australia Pty Ltd
ABN 58 097 064 330
Level 3
390 St Kilda Road
Melbourne VIC 3004
Australia

New Zealand Sponsor
Hospira NZ Limited
23 Haining Street
Te Aro
Wellington
New Zealand

Date of TGA approval: 9 December 2002

Date of most recent amendment: 03 September 2007

DBL® is a registered trade mark of Hospira Australia Pty Ltd