



London, 22 October 2002
EMEA/25175/02

**EMEA PUBLIC STATEMENT ON PARECOXIB SODIUM (Dynastat/Rayzon/Xapit)
RISK OF SERIOUS HYPERSENSITIVITY AND SKIN REACTIONS**

The European Medicines Evaluation Agency (EMEA) and its scientific committee (CPMP) have been made aware of reports of serious hypersensitivity reactions (anaphylaxis and angioedema) and serious skin reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme and exfoliative dermatitis in patients treated with valdecoxib, a selective COX-2 inhibitor. Some of these reactions have occurred in patients with a history of allergic-type reactions to sulphonamides. Valdecoxib is the active metabolite of Parecoxib sodium. It is therefore possible that such reactions may also occur with use of Parecoxib sodium. Parecoxib sodium is indicated in the short-term treatment of postoperative pain. Within the EU¹ it is marketed as an intravenous or intramuscular injection in Austria, Denmark, Finland, Germany, Ireland, Netherlands, Portugal, Sweden, United Kingdom and also in Norway.

Valdecoxib received a positive opinion² by the CPMP on 25 July 2002 and is currently awaiting the European Commission Decision (i.e. it is not in therapeutic use in the EU). It is already marketed in the United States and a number of other markets outside the European Union.

The EMEA wishes to point out the following important safety information:

For physicians considering therapy of patients with parecoxib sodium (Dynastat/Rayzon/Xapit):

- This product is contraindicated in patients with a history of hypersensitivity to sulphonamides
- In post marketing experience, hypersensitivity reactions including anaphylaxis, angioedema and serious skin reactions including erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported in association with valdecoxib.

Information for patients:

- If you have had allergy to antibiotics called “sulphonamides”, you may be prone to severe side effects with parecoxib (Dynastat/Rayzon/Xapit).
- **If you experience**
 - Skin rash, swelling of the face, lips and tongue, wheezing, difficulty in breathing or swallowing or
 - Swelling, blistering or peeling of the skin,**tell your doctor, pharmacist or nurse immediately**

As an urgent measure, the prescribing and patient information of Parecoxib have been modified through a rapid procedure at the request of the Marketing Authorisation Holder. Relevant changes to

¹ On 22 March 2002, the European Commission issued a Marketing Authorisation valid throughout the European Union for the medicinal product Dynastat/Rayzon/Xapit, which contains Parecoxib. The Marketing Authorisation Holder responsible for this medicinal product is Pharmacia.

² Valdecoxib (Bextra/Valdyne/Valdecoxib Pfizer and Kudeq, Valdecoxib Pharmacia Europe EEIG) received on 25 July 2002 a positive opinion for the following indications: Symptomatic relief in the treatment of osteoarthritis or rheumatoid arthritis and the treatment of primary dysmenorrhoea.

the product information are indicated below. The complete revised product information is available in the European Public Assessment Report of Dynastat/Rayzon/Xapit published on the EMEA Website. The product information of Valdecoxib will be equally revised to include the new safety information.

For further information contact:

Mr Noël Wathion

Head of Unit Evaluation of Medicines for Human Use (Tel: +44 20 7418 8592, Fax: + 44 20 7418 8668)

**PROVISIONAL CHANGES INTRODUCED
TO INFORMATION FOR PATIENTS AND PRESCRIBERS AND LABELLING
Dynastat 20 mg powder for solution for injection**

INFORMATION TO PRESCRIBERS

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients. (see section 6.1).

History of hypersensitivity to sulphonamides (see sections 4.4 & 4.8)

Patients who have experienced bronchospasm, acute rhinitis, nasal polyps, angioneurotic oedema, urticaria or allergic-type reactions after taking acetylsalicylic acid or NSAIDs or other cyclooxygenase-2 (COX-2) selective inhibitors.

The third trimester of pregnancy and breast-feeding. (see sections 4.6 and 5.3)

Severe hepatic impairment (Child-Pugh > 9).

Active peptic ulceration or gastrointestinal bleeding.

Inflammatory bowel disease.

Severe congestive heart failure.

4.4 Special warnings and special precautions for use

There is limited clinical experience with Dynastat treatment beyond two days.

Dynastat has been studied in dental, orthopaedic, gynaecologic (principally hysterectomy) and coronary artery bypass graft surgery. There is little experience in other types of surgery, for example gastrointestinal or urological surgery.

Hypersensitivity reactions (anaphylaxis and angioedema) have been reported in post-marketing experience with valdecoxib, and cannot be ruled out for parecoxib (the prodrug of valdecoxib – see section 4.8). Some of these reactions have occurred in patients with a history of allergic-type reactions to sulphonamides (see section 4.3).

Dynastat should be used with caution to treat pain following coronary artery bypass graft surgery as these patients may have a higher risk of adverse events, such as cerebrovascular accident, renal dysfunction or sternal wound complication (infection, dehiscence), especially those with a history of cerebrovascular disease or with a body mass index > 30 kg/m². (see section 4.8)

Since prostaglandin synthesis inhibition may result in deterioration of renal function and fluid retention, caution should be observed when administering Dynastat in patients with impaired renal function (see section 4.2) or hypertension, or in patients with compromised cardiac or hepatic function or other conditions predisposing to fluid retention.

Caution should be used when initiating treatment with Dynastat in patients with dehydration. In this case, it is advisable to rehydrate patients first and then start therapy with Dynastat.

Dynastat should be used with caution in patients with moderate hepatic impairment (Child-Pugh 7-9). (see section 4.2)

Dynastat may mask fever. (see section 5.1) In isolated cases, an aggravation of soft tissue infections has been described in connection with the use of NSAIDs and in nonclinical studies with Dynastat. (see section 5.3) Caution should be exercised with respect to monitoring the incision for signs of infection in surgical patients receiving Dynastat.

Upper gastrointestinal perforations, ulcers or bleeds (PUBs) have occurred in patients treated with Dynastat. Therefore, caution should be taken in patients with a history of PUBs.

Because of its lack of effect on platelets, Dynastat is not a substitute for acetylsalicylic acid for cardiovascular prophylaxis.

Caution should be exercised when co-administering Dynastat with warfarin. (see section 4.5)

The use of Dynastat, as with any medicinal product known to inhibit COX-2, is not recommended in women attempting to conceive. (see sections 4.6 and 5.1)

4.8 Undesirable effects

Of the Dynastat treated patients in controlled trials, 1962 were patients with post-surgical pain.

The following undesirable effects had a rate greater than placebo and have been reported among 1543 patients administered Dynastat 20 or 40 mg as a single or multiple dose (up to 80 mg/day) in 12 placebo controlled studies, including dental, gynaecologic, orthopaedic surgery or coronary artery bypass graft surgery as well as pre-operative administration in dental and orthopaedic surgeries. The discontinuation rate due to adverse events in these studies was 5.0 % for patients receiving Dynastat and 4.3% for patients receiving placebo.

Common ($\geq 1/100$, $<1/10$)

Autonomic Nervous System Disorders: hypertension, hypotension.

Body as a Whole - General Disorders: back pain, peripheral oedema.

Central and Peripheral Nervous System Disorders: hypoaesthesia.

Gastro-intestinal System Disorders: alveolar osteitis (dry socket), dyspepsia, flatulence.

Metabolic and Nutritional Disorders: creatinine increase, hypokalaemia

Psychiatric Disorders: agitation, insomnia.

Red Blood Cell Disorders: post-operative anaemia

Respiratory Disorders: pharyngitis, respiratory insufficiency.

Skin and Appendages Disorders: pruritus.

Urinary System Disorders: oliguria.

Uncommon ($\geq 1/1,000$, $<1/100$)

Autonomic Nervous System Disorders: aggravated hypertension.

Body as a Whole - General Disorders: abnormal sternal serous wound drainage, wound infection.

Gastro-intestinal System Disorders: gastroduodenal ulceration

Heart Rate and Rhythm Disorders: bradycardia.

Liver and Biliary System Disorders: SGOT increased, SGPT increased.

Metabolic and Nutritional Disorders: BUN increased.

Platelet, Bleeding and Clotting disorders: ecchymosis, thrombocytopenia

Vascular (Extracardiac) Disorders: cerebrovascular disorder.

The following rare, serious adverse events have been reported in association with the use of NSAIDs and cannot be ruled out for Dynastat: acute renal failure, congestive heart failure, **anaphylactic shock**, bronchospasm, hepatitis.

Following coronary artery bypass graft surgery, patients administered Dynastat may have a higher risk of adverse events, such as cerebrovascular accident, renal dysfunction or sternal wound complication.

In post marketing experience, the following reactions have been reported in association with the use of valdecoxib, and cannot be ruled out for parecoxib: Anaphylactic reactions, angioedema, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis (see sections 4.3 & 4.4).

INFORMATION TO PATIENTS:

2. BEFORE YOU ARE GIVEN Dynastat

You will not be given Dynastat...

- **If you have had an allergic reaction to a group of medicines called “sulphonamides” (some antibiotics used to treat infections, e.g cotrimoxazole, sulphasalazine).**
- **If you are allergic to parecoxib** or any of the other ingredients of Dynastat (see blue-shaded area, below left).
- **If you are allergic or have ever had reactions to acetylsalicylic acid or ~~or similar medicines for pain~~ to other NSAIDs (e.g ibuprofen), or similar medicines for pain (ibuprofen, for example).** Reactions might include wheezing (*bronchospasm*), badly blocked nose, itchy skin, rash or swelling of the face, lips or tongue, other allergic reactions or nasal polyps after taking these medicines.
- **If you are in your last three months of pregnancy**
- **If you are breast-feeding**
- **If you have severe liver disease.**
- **If you have an active stomach ulcer or bleeding in the stomach or intestines**
- **If you have inflammatory bowel disease**
- **If you have severe congestive heart failure**

If any of these applies to you, you will not be given the injection. **Tell your doctor or nurse immediately.**

4. POSSIBLE SIDE EFFECTS

Some people given Dynastat can have side effects. If you notice any of these, or any other effects of the injections not mentioned, **tell a doctor or nurse, as some of these effects may be serious enough to require immediate medical attention.**

More common effects

These could affect between 1 and 10 in every 100 people

- Blood pressure may be made higher or lower
- You may get back pain
- Ankles, legs and feet may swell (fluid retention)
- You may feel numb
- You may get stomach ache, indigestion, bloating and wind
- Tests may show abnormal kidney function
- You may feel agitated or find it hard to sleep
- There is a risk of anaemia
- You may get a sore throat or difficulty breathing
- Your skin may be itchy
- You may pass less urine than usual.

> **If any of these affects you, talk to your doctor or nurse.**

Uncommon effects

These could affect less than 1 in every 100 people

- The heart may beat more slowly
- Blood tests may show abnormal liver function
- You may bruise easily (or have a low blood platelet count)
- Surgical wounds may become infected
- There is a risk of stroke.

> **If any of these affects you, talk to your doctor or nurse.**

Rare Effects

These could affect less than 1 in every 1000 people.

- Allergic reactions such as skin rash, swelling of the face, lips and tongue, wheezing, difficulty breathing or swallowing
- Swelling, blistering or peeling of the skin.

> **If any of these affects you, talk to your doctor or nurse.**