DIPYRONE

A drug NO one needs

Dipyrone - one of the world's most widely used painkillers carries unacceptable risks. Dipyrone is not needed and should no longer be used.

This book explains why.

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Dipyrone: A drug no one needs

Andrew Chetley 1993

Prepared for Health Action International

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Introduction

A survey of commercial prescribing guides in 12 areas of the world showed that in 1987-8, out of 1739 analgesics marketed 26% contained dipyrone. In fact dipyrone was the second most frequently used ingredient after paracetamol. It might be assumed that the safety of such a drug was we]] established but this is not the case. On the contrary there is a clearly proven link between dipyrone use and serious adverse effects including agranulocytosis and shock. Dipyrone has no therapeutic advantages over other, much safer, analgesics. It is an unacceptably dangerous drug which we do not need.

This document is published by BUKO Pharma-Campaign and HAl-Europe as part of their campaign for rational drug use. It contains the following three sections:

1) A review of dipyrone;
2) A survey of dipyrone-containing products from 12 areas of the world;
3) An annotated bibliography of original articles, reports and reviews on dipyrone.

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The Federal Congress of Development Action Groups (BUKO) is a network of around 300 Solidarity Groups in the Federal Repuhlic of Germany. In 1980 BUKO started a campaign against the global malpractices in drug marketing by the multinational pharmaceutical companies. BUKO was one of the co-founders of Health Action International

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A drug no one needs

Dipyrone is an analgesic (pain killer) with antipyretic properties (effective against fever). Confusion occurs because it is known by many names: metamizol, novaminsulfonicum, noramidazophenum, noraminophenazonum, novamidazofen, methampyrone, sodium noramidopyrine methanesulphonate, sulpyrine, and in India analgin.

Like propyphenazone, aminopyrine and phenylbutazone it is a member of the pyrazolone group of compounds. But in contrast to phenylbutazone the anti-inflammatory properties of dipyrone are limited. As the sodium sulphonate derivative of aminopyrine, dipyrone has the advantage of being soluble which al1ows the production of highly concentrated solutions up to 50%. Effective doses of dipyrone can therefore be injected intravenously to relieve acute pain, and this has made dipyrone-containing drugs popular in some countries for the relief of biliary and ureteric colic.

The largest dipyrone manufacturer, the German multinational company Hoechst, claims an additional spasmolytic effect of the drug which would offer a therapeutic advantage in colic. But there is no convincing scientific proof that therapeutic doses have a direct spasmolytic effect[1]• p70) Even the pharmacologist Prof. Forth who originally supported the theory of a direct spasmolytic effect of dipyrone, has in the meantime adopted a more sceptical position. ' There is no doubt that high doses are needed (for a spasmolytic effect) ... No reasonable person would expect a spasmolytic effect of dipyrone in therapeutic doses, e.g. after an oral dose of 0.5 to 1 gram.' (2. p141)

The drug was introduced by Hoechst in 1922, but essential pharmacological and toxicological data are still lacking. Nowadays such a poorly documented drug would hardly be licensed. The fact that so little is known about dipyrone is worrying because it causes very serious adverse effects (agranulocytosis* and shock).

But according to Dr. R. Timmers from Hoechst, dipyrone has an 'outstanding safety margin' and 'has proven itself since more than 60 years to be an effective and at the same time outstandingly well tolerated analgesic substance'. (3)

Nevertheless, in the Federal Republic of Germany the use of dipyrone was heavily restricted by the Federal Health Office (Bundesgesundheitsamt, BGA) in 1982 and 1986 because of its life-threatening risks. Dipyrone may now be used only for acute severe pain after trauma or surgery, colic, cancer pain, other acute or chronic severe pain when other drugs are contra-indicated, and in cases of high fever that do not respond to other measures. The registration of combinations of spasmolytic substances with dipyrone (e.g. Baralgan, Buscopan Compositum, Avafortan) was suspended because the additional components might add further risks. Manufacturers were requested to provide scientific proof by the end of 1988 that combinations of dipyrone with spasmolytics have an additional therapeutic effect without increasing risks. Hoechst voluntarily withdrew its dipyrone combination,

* Agranulocytosis is lack of granulocytes - the white blood cells which are an important defence against invading bacteria. It can be fatal.

Baralgin, from the German market in January 1987, before the March dead-line. Boehringer Ingelheim did not succeed in providing evidence of additional therapeutic effect and has now definitively withdrawn its combination product Buscopan Compositum.(4)

Apart from combinations of dipyrone with spasmolytics all other combinations have been definitively banned by the BGA. Additionally, the German Federal Health Ministry put all dipyrone containing drugs on prescription from January 1, 1987. This was done on the advice of the Federal Health Office. Dipyrone has been banned or severely restricted in Australia, Bangladesh, Canada, Denmark, Egypt, the Federal Republic of Germany, Greece, Ireland, Israel, Italy, Japan, Malaysia, New Zealand, Norway, the Philippines, Saudi Arabia, Singapore, Sweden, the US, and Venezuela.(5) Combination products containing dipyrone have been banned in Pakistan.

Bad health - good business

There may be no medical or scientific case for the ,drug, but there is a business case. In 1987, two of Hoechst's dipyrone products Novalgin and Baralgin brought in more than US $ 190 million, just over 5% of the company's total world drug sales.(6) Although sales of Novalgin in Germany were 'virtually halved' during the year, following the restrictions on indications announced in late 1986, the company said that in other countries throughout the world there was still 'a great deal of confidence in Novalgin'. Because dipyrone is banned or restricted in many industrialized countries most of the sales are in the third world. Hoechst India achieved 42% of its pharmaceuticals sale volume in the first four months of 1986 with only two drugs': Baralgan and Novalen. In Latin America Novalgina alone brought in one third of the pharmaceutical revenue. Furthermore Novalgina was the top selling drug in Latin America in 1985, with sales of US $ 30 mil1ion.(7)
A survey of prescribing guides in 12 areas of the world found that in 1987-8, out of 1739 analgesics, 26% contained dipyrone. In fact, dipyrone was the second most frequently used ingredient in pain killers, after paracetamol.
In 1984, a survey in Peru found 28 products containing dipyrone, and more important, that 73% of the drugs used for pain or fever contained dipyrone.(8)

Number of analgesic preparation containing dipyrone in 12 regions of the world (1987-1988)		
Country/region, prescribing guide, date	# analgesics	#Dipyrone preparations
Africa, *MIMS Africa* May 1988	126	21
Brazil *DEF* 1987-88	262	155
Caribbean *MIMS Caribbean* May 1988	68	12
Hong Kong *HKIMS* April 1988	80	5
India *MIMS India* Feb 1988	73	18
Indonesia IIMS Feb 1988	176	63
Mexico DEF 1987	153	92
Middle East *MIMS Middle East April* 1988	146	24
Pakistan *QIMP* 1987	206	26
Philippines *PIMS* April 1988	179	6
South Africa *MIMS* May 1988	135	8
Thailand *TIMS* March 1988	135	30
TOTALS:	1739	460

The 'Boston' study

It is easy to understand that dipyrone manufacturers led by Hoechst defend such a profitable source of income. Dipyrone-induced agranulocytosis led to the ban in many countries and it was therefore in Hoechst's interest to play down this risk. As early as 1978 Hoechst asked the Boston University Drug Epidemiology Unit in the US to investigate the relation between dipyrone use and the risk of agranulocytosis. Finally a contract was signed to evaluate the risks of agranulocytosis and aplastic anaemia in relation to analgesic drug use.

A first report of the International Agranulocytosis and Aplastic Anemia Study IAAAS (also referred to as the 'Boston study') was published in 1986.(9) The intention was to publish the complete study with all data as a book in 1989.

The Boston study aimed to collect all cases of agranulocytosis and aplastic anaemia that were admitted to hospital (community cases) or occurred during a stay in hospital (hospital cases) in eight locations: Israel, Barcelona, Ulm, West Berlin, Milan, Budapest, Sofia and Stockholm Uppsala, with a total population of 22.3 million people. Attempts to collect data in Brazil and Indonesia were abandoned because it was not possible to ensure that the data were reliable. Only five of those locations - Israel, Barcelona, Ulm, West Berlin and Budapest - were used for the calculations on dipyrone-induced agranulocytosis.

There is no doubt that the Boston study was better designed than many previous evaluations of drug risks. Dr. Faich from the office of epidemiology and biostatistics of the US Food and Drug Administration (FDA) describes the study as 'extraordinary': 'The presentation of an impressive pharmaco-epidemiologic study reminds us how few such studies are carried out.' (10)
Because the methods used in calculating the risks are not adequately described in the preliminary report and the raw data have not been published at all this appreciation is obviously only meant for the study design and the enormous work involved in it.

The results of the preliminary report on the study provoked critical comments. Indeed, the first questions were asked by Dr. Faich in his editorial on the Boston study: 'Considerable variation by region in the risk ratios for dipyrone was found and discussed, but it remains unexplained and disturbing. While the variation may be due to differences in populations or medical practice, one must be concerned about hidden biases or methodological problems that could affect other results of the study.' (10)
The disturbing result was that in three of the locations Ulm, Berlin and Barcelona the risk of contracting agranulocytosis was 23.7 times higher from using dipyrone than from not taking the drug. However, in Israel and Budapest, the relative risk was, in contrast to the other locations, less than 1.

Dr. van Dijke from the Netherlands Centre for Monitoring of Adverse Reactions to Drugs questioned the method of calculation used as unsuitable to the study of a disease (agranulocytosis) that is largely drug-induced and interpreted the considerable variation of the risk ratios as a consequence of an inappropriate methodology. He also criticised the authors' decision to compare the risk of agranulocytosis due to dipyrone with the risk of

a granulocytosis due to other drugs, because this results in a gross underestimate of the real risk. Comparison with 'spontaneous' agranulocytosis was needed to give the real risk of dipyrone. (11)

Other critics seriously doubted whether the ambitious approach of the study design was realistic. The Boston study is a population-based, retrospective case-control study. 'Such a case-control study requires a catch population which has to be geographically well-defined and should remain stable in its composition throughout the study ... *All the hospitals and clinics* which recruit their patients from this catchment area *must participate* in such a study so that no case will escape the screening programme.' (12) Because Dr. Faich was so impressed by this study design he commented: 'This enormous study sought all cases in a total defined population of 22.3 million so that reasonable estimates of incidence could be derived.' (10)

But there are reasons to doubt whether *all* cases of agranulocytosis in that vast catchment area could be found. A group of biostatisticians, one of them based in a regional centre of the Boston study (Ulm, West Germany), wrote in a letter to JAMA, the journal which published the IAAAS report: 'There is no doubt that all cases in the study are true cases of agranulocytosis, but it is extremely difficult to detect every case in a population of 22.3 million ... not all hospitalized patients will have been registered in each of the large number of about 300 participating hospitals, despite the telephone calls of the regional centers to the participating hospitals.' (13) Justification of this doubt can be found in the authors' own response, describing the Swedish data included in the lAA.AS study: 'In Stockholm, Bengt-Erik Wiholm, MD, examined available computer records. In 1983 through 1984, we identified 19 cases; the files yielded an additional four.' (14)

Additionally, serious doubts were raised whether the regions were really well defined and the population figures correctly calculated. Dr. Leo Offerhaus, who formerly worked with the Dutch registration authority, stated after noting the official population figures for the region of Ulm that **'the number of 5,300,000 inhabitants, quoted to live in the Ulm region, has not been adequately explained. The Baden-Wurttemberg census authority has called this number grossly exaggerated ('weit Uberhoht').'** Dr. Offerhaus calculated on the basis of the official population data and the regional coverage of the service of adjoining large and renowned university hospitals that the hospitals of the Ulm region served about 786,000 people.(15) The large difference between the two figures in the IAAAS and from Dr. Offerhaus would certainly affect the calculations and results of the Boston study.

The difficulties of detecting all cases of agranulocytosis in a large number of hospitals and of defining the limits of the regions (West-Berlin being the only clear-cut region, since it is surrounded by a wall) were not the only problems. It is also difficult to find out by questioning patients whether they had taken dipyrone. A study in West-Berlin compared the history of analgesic use obtained from the patients with the results of urine analysis and found 'that analgesic users tend either to deny drug intake or to give incorrect information about the kind and extent of their analgesic intake',(16) The reliability of the information given by patients could hardly have been improved by presenting them with a list of brand names of dipyrone drugs: even in 1986 there were still 247 different brands of such drugs on the German market. For this reason the questionnaire used in the study mentioned only 'names that together accounted for over 90% of the sales of the common non-narcotic

analgesic drugs (there were too many trade names to ask about the remaining 10%) as well as other drugs generally suspected of causing either dyscrasia'. (9)

For these reasons the incidence figures given in the Boston study cannot be regarded as realistic. The statement 'that in Ulm, Berlin, and Barcelona, if **1** million persons are exposed to dipyrone for up to one week, one person will develop agranulocytosis as a consequence' (14) seems particularIy untrustworthy. As The Lancet subsequently pointed out: ‘The calculation underlying this estimate is not explained. The peculiar denominator is difficult to apply to real life. The risk for exposure during one year could be up to 50 times higher. It would be expressed more clearly as the number of cases per million defined daily doses (DDD), or per 100,000 packs sold.’ (17)

From the medical point of view Dr. Del Favero summarized the main message of the Boston study in his special review for the authoritative Side Effects of Drugs Annual: 'The study confirmed that dipyrone can induce agranulocytosis. It has been found responsible for about a quarter of the drug-induced cases in the participating countries; in some regions patients who had taken dipyrone in the previous week were 20-30 times more likely to develop agranulocytosis than non-takers.' (18)

Misleading interpretation

These critical statements put into perspective the defensive argument put forward by Prof. Gareis, the Hoechst director concerned: 'What the Boston study has already shown, despite all criticism, is that ... the risk is certainly no greater than it was in 1981, at the time of the first hearing by the German Federal Drug Authority BGA' (its estimate of the risk of agranulocytosis due to dipyrone was 1:30,000).(19) Other representatives of Hoechst found the results less problematic and declared that the risk of dipyrone-induced agranulocytosis 'has now been quantified' and is 'extremely low', and claimed that this had been the main 'problem' with dipyrone for over 40 years and this problem was now 'solved'. Hoechst's marketing director, Dr. HansGunther Grigoleit, said 'in view of the improved risk/benefit situation of dipyrone, there's no need to change the legal status of dipyrone towards more restrictions'.(20)

Dr. Del Favero has described this interpretation as 'misleading' and pointed out that 'since safer and equally effective drugs exist for the main indications of dipyrone (i.e. paracetamol and salicylates), dipyrone use should be at least restricted to patients who cannot use the above-mentioned drugs. Unfortunately the drug is still freely available over-the-counter in many developing countries and even in some countries in Europe.' (18)

In contrast to Dr. Grigoleit, in its decision after the 1986 hearing, the BGA came to the conclusion that the estimate of the risk by the Boston study confirmed its own estimate made in 1981: ‘The results of the Boston study have confirmed the suspicion of the particularly serious risk of agranulocytosis which the BGA in 1981 considered well founded, though it was described (by the company) as based on a speculative estimate. The results of the hearing of 1986 compel us to conclude that the estimate of incidence based on the results of the Boston study is a minimum estimate. It is reasonable to assume that the true figure is higher. According to one

expert's estimate the true figure is likely to be 3 to 5 times as high even if undetected cases are not allowed for.' (21)

Dr. Leo Offerhaus concluded that 'the study proved beyond all doubt the causative role of dipyrone in the development of agranulocytosis, a syndrome which after use of this particular drug has an overall mortality of approximately 25%. Many have, not unfairly, criticized the way in which the incidence of the risk was calculated, the calculation methods used and the data on which the calculations were based. In retrospect it seems questionable whether the study plan was at all suitable to compute incidence and risk data relating to single drugs. The IAAAS study is in itself eminent and very useful, but would have been better off if the main reason for performing it, i.e. absolving dipyrone, had been less forcefully stressed.' (15)

Shock: another life-threatening risk

The discussion about the Boston study and the haematological risks should however not lead us to neglect the cardiovascular risks. Even the honorary advisory committee of the Boston study has warned 'that any evaluation of the safety of a given analgesic must take into consideration not only its haematological side-effects but also its other side-effects'.(22)

Anaphylactic shock from pyrazolone drugs was first reported in 1958.(23)
In 1983 a group of Swiss authors published a systematic analysis of an cardiovascular reactions to intravenous dipyrone.(24) A fall in blood pressure was found in 7 of 2053 patients given a dipyrone preparation i.v., a frequency of 0.34%. In 6 of these 7 patients the blood pressure took longer than 10 hours to recover. In 5 of them the systolic pressure was still below 100 mm Hg after 10 hours.

Already in 1981 the Medicines Commission of the German Medical Association had politely reminded doctors about essential precautions: 'Prescribing physicians ... are aware that in rare cases hypersensitivity reactions can occur and may amount to severe anaphylactic shock with possibly fatal outcome. They are therefore well prepared for the treatment of anaphylactic shock, especially after intravenous injection (of dipyrone).' (25)

At the end of 1987 the Medicines Commission of the German Medical Association warned the profession not to use dipyrone injection as a first-line analgesic, even for severe pain (the remaining indication): 'Renal or biliary colic kills no one. For this reason even a small risk of a life-threatening condition ... is an unacceptable price to pay for pain relief, especially since it cannot be maintained that alternatives are not available.' (26)

It could hardly have been put more plainly: dipyrone is no longer an acceptable drug. As Dr. Offerhaus stated: 'dipyrone is a drug for which there is no obvious need (certainly not as an OTC analgesic), and for the restricted indications for which it might be useful, less dangerous alternatives are available'.(15)

Aggressive marketing in the third world

The aggressive marketing of dipyrone-containing drugs in the third world is thus completely indefensible. Companies have been recommending dipyrone for everything from headaches to labour pains, as the following examples shows.

In the Philippines during April 1988, Winthrop's Gardan was recommended for 'headache, toothache, neuralgia, rheumatism, lumbago, and pain associated with colds, influenza, pneumonia and other infectious diseases'; Sandoz/Wander's Gifaril was indicated for 'pain, fever'; Lagap's Lagalgin was recommended for 'headache, muscular pain, neuralgia, sciatica, lumbago, spastic dysmenorrhoea (menstrual pain), labour pains, biliary colic, neuritis, traumatic pain in injuries, post-operative pains, rheumatism, arthritis, carditis, chronic polyarthritis'; and Hoechst's Melubrin was indicated for 'various kinds of pain. Muscular and articular rheumatism; influenza and febrile conditions.' (27)

In an African prescribing guide in March 1989, Hoechst's Novalgin was recommended for ‘pains, fever, spasms’.(28) In South Africa in April 1988, Hoechst's Baralgan included ‘dysmenorrhoea’ among its indications.(29)

In Thailand in March 1988, Thai Nakorn Patana's Acodon was recommended for the all-inclusive 'analgesic, headache and antipyretic'; Winthrop's Conmel for ‘pain and/or fever, cephalgia, sciatica, neuralgia, in rheumatic conditions, for dental procedures requiring analgesia’; Westmont's Deparon for ‘headache, neuralgia, dysmenorrhoea’; General Drugs House's Genergin for ‘headache, toothache, menstrual pain ... to reduce fever due to common cold’; Chew Brother's Invogin for ‘relief of pain, fever, neuralgia, trauma, sciatica, dysmenorrhoea’; Hoechst's Novalgin for ‘various kinds of pain ... influenza and febrile infections’; ‘spasmodic pain in female reproductive organs’ was included among the indications of Hoechst's Baralgan; and Siegfried's Pyralgin for the open-ended ‘painful conditions of any origin’,(30)

In India in February 1988, Concept's Anadex was indicated simply for ‘pain’; Asta Werke's Avafortan was advertised with the claim that it 'removes all colic and smooth muscle spasms in 3 minutes or less'; Hoechst's Baralgan was recommended for 'dysmenorrhoea' and Novalgin for ‘pain, fever’; Alkem's Pamagin for ‘aches & pains associated with anxiety & tension, dysmenorrhoea’. IDPL's Spasmizol for ‘pain, spasms’; and Rallis' Zimalgin-A for ‘moderate to severe pain’.(31)

In Indonesia in February 1988, Soho's Antalgin was recommended for ‘neuralgia, headache, sciatica, various kinds of pain’ and Winthrop's Beserol for ‘premenstrual tension & dysmenorrhoea’,(32)

In Pakistan in 1987 Hoechst advertised Baralgin as an ‘ideal adjunct in antidiarrheal therapy’ under the headline ‘Baralgin for faster relief when it counts’.

In Colombia in 1988, Winthrop's Conmel was indicated for ‘symptomatic treatment of all acute pain and fever (influenza, pneumonia and other infectious diseases); general alleviation of acute and chronic pain of mixed etiology (cephalgia, sciatica, neuralgia and in the treatment of various kinds of

rheumatism); after tooth extraction, in toothache, postoperative pains and for all dental procedures requiring analgesia'; Sandoz/Wander's Gifaril was indicated for 'febrile conditions, diverse pains, toothaches'; Knoll's Neosaldina was simply recommended as an 'analgesic, antispasmodic and antipyretic'; and Merck's Sistalgin Compositum was described as a 'spasmolytic analgesic', indicated in 'colic and pains of any origin'.(33)

In Brazil in 1988, Hoechst recommends its Novalgina as successful therapy in 'painful conditions and in fever of different etiology, like cephalgia, neuralgia, sciatica, lumbago, influenza and cold'; for its injectable form the users are additional1y advised that 'in muscular and articular rheumatism high parenteral doses should be used'; Hoechst's injectable Baralgin is indicated for 'spasms of smooth muscles: renal colic, ureteric spasms, spasms of the urinary bladder, biliary colic, dyskinesia of the biliary duct, intestinal spasms of any origin and spasmodic dysmenorrhoea. Asthmatic attacks of moderate intensity can be shortened by injection'; Searle's Fluviral contains. dipyrone, mepyramine, caffeine and phenylpropanolamine (DL-norephedrine) and is recommended for the 'symptomatic treatment of influenza and cold'; Merck's Mio-Citalgan, a mixture of the vitamins B1, B6, B12, caffeine, an antispasmodic and dipyrone, is indicated in 'lumbalgia, sciatica, torsions, luxations, muscular distensions, torticollis, cervical syndrome, arthritis and arthrosis, bursitis, tendinitis and synovitis, myositis and fibrositis'; Knoll's Neosaldina is recommended for 'spasms of functional and organic origin, gastrointestinal, biliary and ureteric colic, dysmenorrhoea, headache, muscular pain, neuralgia, toothaches, influenza and cold'.(34)

Trying to preserve the market

Since 1986, Hoechst and many other companies have been trying to convince prescribers and drug regulatory authorities, particularly in developing countries, that dipyrone is a 'safe' drug. In Thailand, Hoechst's Manager, Phornvit Phacharintanakul, said that the company believed that Baralgan 'scientifically and technically speaking, will pose no problem to users' and said that Hoechst had withdrawn the drug in Germany 'in view of the political situation' in the country 'and not because of the adverse effects of the drug'. (35) To reinforce the message, Dr R.Timmers, the head of the Medical Affairs division in Hoechst's German headquarters, visited Thailand several times and toured medical and pharmaceutical schools giving presentations on the Boston study, in which he claimed that dipyrone was as 'safe as aspirin'. At the same time, Hoechst distributed copies of the Boston study, carefully highlighted to draw attention to its more favourable messages. In early 1988, Hoechst distributed another publication to physicians in Thailand which included a copy of the Thai package insert for Baralgan and what purported to be the German package insert for Baralgin, in an effort to demonstrate that the company operated a single standard of drug information worldwide. However, the supposed German package insert turned out to be an internal information sheet and differed considerably from the one approved for use in Germany by the BGA. The differences included more indications and fewer warnings. This 'error' in information was confirmed in April 1988 when the Thai manager, Phornvit, attended a seminar in Germany, organised by the Association of German Pharmaceutical Industries. ([36]) By October 1988 Hoechst Thailand had sent no correction of this false information to Thai physicians.

With this irresponsible overpromotion, it is little wonder that products containing dipyrone have become so popular in many countries of the third world, generally available without the need of a prescription. This aggressive marketing is particularly worrying because the risks of dipyrone in the Third World are likely to be more serious than in the countries involved in the Boston study. The authors of the study themselves point out that ‘inferences about the public health impact of analgesic use cannot be more widely generalized to other regions of the world if a fatal outcome of agranulocytosis is more common because of factors such as malnutrition or inadequate medical care'.(9), p1756)

Dipyrone is not a safe drug. It is not an essential drug. It offers no significant therapeutic benefit for the high risk it presents. It is time that it was removed from the world market.

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32.IIMS, Feb 1988
33. Diccionario de Especialidades Farmaceuticas, 16a.edicion, Colombia, 1988.
34.Diccionario de Especialidades Farmaceuticas, 17.a edicao, 1988/89.
35. Thanong, K, 'Hoechst asserts its drug not harmful', The Nation (Thailand), 22 Oct 1987, p.19.
36. Junkyard Thailand: Dumping of drugs and double standards in drug information: the case of dipyrone, Bangkok, Drug Information for Action Centre, 1988, pp.40-1; Bundesverband del' Pharmazeutischen Industrie (ed), Arzneimittelversorgung in del' Dritten Welt Ziele, Realitaten, Notwendigkeiten, Seminar des Bundesverbandes del' Pharmazeutischen' Industrie am 18.ApriJ 1988 in FrankfurtlMain, p. 68 .

Dipyrone: an annotated list of current articles

(The items marked * in this list are collected in a pack available from HAl)

The IAAAS: publications, discussion, critiques

• The International Agranulocytosis and Aplastic Anemia Study. The design of a study ofthe drug etiology of agranulocytosis and aplastic anemia. Eur J Clin Pharmacol1983; 23: 833-36.
• Shapiro S. Agranulocytosis and pyrazolone. Lancet 1984; 1: 451-452. (letter) // An interim report on the IAAAS.
• Herxheimer A, Yudkin J. Agranulocytosis and pyrazolonc analgesics. Lancet 1984; 1: 730. (letter) // Disputes Shapiro's claim that IAAAS data win permit calculation of the true incidence of agranulocytosis.

* The International Agranulocytosis and Aplastic Anemia Study. Risks of agranulocytosis and aplastic anemia: a first report of their relation to drug use with special reference to analgesics. JAMA 1986; 256: 1749-1757.
* Faich GA. Analgesic use and pharmacoepidemiology. JAMA 1986; 256: 1788, (editorial)
* Dijke CPH van. Analgesic use, agranulocytosis, and aplastic anemia. JAMA 1987; 257: 2590. (letter)
* Feldman U, Gaus W, Kretschmer FJ, Repges R. [same title] JAMA 1987; 257: 2590-91. (letter)
* Kumana C. [same title] JAMA 1987; 257: 2591. (letter)
* Levy M, Shapiro S. Kaufman DW,Kelly JF. [same title] JAMA 1987; 257: 2591-92, (reply)
• Weerasinghe WMT. Commentary from Southeast Asia. JAMA SEA February 1987: 30.

* Editorial. Analgesics, agranulocytosis and aplastic anaemia: a major case-control study. Lancet 1,986; 2: 899-900.
* Levy M, Shapiro S. Safety of dipyrone. Lancet 1986; 2: 1033-34. (letter) // Criticises a point in the preceding editorial.
* Doll R, Lunde PKM, Moeschlin S. Analgesics, agranulocytosis and aplastic anaemia. Lancet 1987; 1: 101. (letter) // Comment on editorial.
• Anon. Hoechst, dipyrone and agranulocytosis: the IAAAS study. Scrip 1986; no 1128: 19-22. /I Reports presentation at Stockholm CPT conference.

• Moeschlin S. (International studies on agranulocytosis and aplastic anaemia through non-narcotic analgesics). Schw Med Wochenschr 1986; 116 (49): 1742. (editorial, in German)
* del Favero A. Analgesic use and risks of agranulocytosis and aplastic anemia. Section of chapter 10 In: Side effects of drugs Annual 11, ed M N G Dukes. Amsterdam: Elsevier 1987; 89-91. // 15 references.
• del Favero A. Uso di analgesici e rischio de agranulocitosi. Ricerca & Pratica 1987; no 13: 9-14. // Italian version of the preceding item.

* Offerhaus 1. Metamizol: een honderdjarige treurnis. (Dipyrone: the sadness of a centenary). Ned Tijdschr Geneesk 1987; 131: 479-81. [*English translation available]
* Levy M, Shapiro S. Reply to Offerhaus. Ned Tijdschr Geneesk 1987; 131: 1680-81.
* Offerhaus L. Rejoinder to above. Ned Tijdschr Geneesk 1987; 131: 1681-83 .

* Kramer MS, Lane DA, Hutchinson TA. Analgesic use, blood dyscrasias, and case-control pharmacoepidemiology: a critique of the International Agranulocytosis and Aplastic Anemia Study. J Chronic Diseases 1987; 40: 1073-81.
* Participants of the lAAAS. Reply to above. JChronic Diseases 1987; 40: 1083-85.

Other epidemiological studies

1952 • Discombe G. Agranulocytosis induced by dipyrone, an avoidable cause of death. Br Med J 1952; 1: 1270-? // Summarises and reviews four earlier series totalling 11 cases (8 deaths) among 1272 patients exposed to dipyrone. (Justly criticised by Hoechst)

1964 • Huguley CH. Agranulocytosis induced by dipyrone, a hazardous antipyretic and analgesic. JAMA 1964; 189: 938-? // Cites Discombe + three American series, i.e. another 127 patients exposed to dipyrone. But no more cases. Incidence thus estimated as 11/1399 = 0,79%. (Justly criticised by Hoechst)

1967 • Gross R, Horstmann H, Vogel J et aI. Zur Epidemiologie und Klinik del' medikamentos-allergischen Agranulozytose. Med Welt 1967; 31: 1767-?

1973 • Bottiger LE, Westerholm B. Drug-induced 'blood dyscrasias in Sweden. Br med J 1973; 2: 339-341.

1979 • Bottiger LE, Furhoff AR, Holmberg 1. Drug-induced blood dyscrasias: a 10-year material from the Swedish Adverse Drug Reaction Committee. Acta Med Scand 1979; 205: 457-61.

• Varonos DD, Santamouris S, Karambali S. The incidence of dipyroneinduced agranulocytosis in Greece during 1975. J Int Med Res 1979; 7: 564-? // Incidence of agranulocytosis appears unrelated to dipyrone use in Israel, ' Australia, Sweden and other countries. (cited by Hoechst)

1980 • Levy M, Kewitz H, Altwein W, HilJebrand J, Eliakim M. Hospital admissions due to adverse drug reactions: a comparative study from Jerusalem and Berlin. Eur J Clin Pharmaco11980; 17: 25-32 ..

1981 • Bottiger LE, Bottiger B. Incidence and cause of aplastic anemia, hemolytic anemia, agranulocytosis and thrombocytopenia. Acta Med Scand 1981; 210: 475-79.

1983 • Shinar E, Hershko C. Causes of agranulocytosis in a hospital population: identification of dipyrone as an important causative agent. Isr J Med Sci 1983; 19: 225-29.// Retrospective study of cases of agranulocytosis from 1970-81,31 of 48 cases 'had drug-induced neutropenia'; 11 oHhese had taken dipyrone in the preceding month, 2 of the 7 deaths from drug-induced neutropenia were attributed to dipyrone.

• Levy M. Causes of agranulocytosis in a hospital population: identification of dipyrone as an important causative agent. Isr J Med Sci 1983; 19: 1110. (letter) // Criticises preceding study as biased because the drug history was not recorded systematically, and because 20% of hospital patients in Israel regardless of diagnosis have recently taken the drug.

• 1987 PaIva ES, Eranko PO. Dipyrone and agranulocytosis in Finland. Tenth International Congress of Pharmacology, Sydney, 28 August 1987; abstract P 1529./ TEXT: *The suspected association of dipyronc and agranulocytosis (AG) has led to its withdrawal in many countries, e.g. Sweden in*]973, *but not in Finland, We analysed all the reports on suspected blood disorders due to NSAIDs + dipyrone submitted to the National Board of Health during the period* 1973-85. *Dipyrone was suspected in* 14 *cases of AG* (.1 *fatal). Other pyrazolones were suspected in* 4 *cases, indometacin in 2 and ibuprofen in 1 case. Aspirin, paracctamol, diclofenac or other NSAIDs were not suspected once. The relative yearly consumption of the suspected*

drug was dipyrone 1, *other pyrazolones* 1, *ibuprofen* 2,5, *indometacin 6. Consequently it can be calculated that dipyrone is 80-50 times more liable to cause AG than ibuprofen or indometacin. The consumption of dipyrone is less than* 3% *of the total NSAID consumption, nevertheless it is suspected of more cases of AG than the rest of the NSAIDs together. Dipyrone was associated with all the fatal cases of NSAID-induced AG. The marketing status of dipyrone in Finland should be seriously questioned.*

Commentaries and reports of official decisions

1979 • Anon. Agranulocytosis door geneesmiddelen (agranulocytosis from drugs). Geneesmiddelenbul!etin 1979; 13: 45-49.

1983 • Offerhaus L. De Russische roulette van de pyrazolonen. (The Russian roulette of the pyrazolones) Ned Tijdschr Geneesk 1983; 127: 638-642. (cites 37 refs) // Author's summary: *Some non-steroidal anti-inflammatory drugs and analgesics belonging to the pyrazolone group have for years been in ill repute because of the not inconsiderable risk of occurrence of severe bonemarrow depression (agranulocytosis and aplastic anaemia) with a high mortality rate. Injudicious w;e, facilitated by the disguise of the active component in combination preparations increases the risk. Since many less dangerous alternatives are available, the use of such drugs for relatively benign conditions should be actively discouraged. The antirheumatic drugs phenylbutazone and oxyphenbutazone should be used only on very strict indications. The analgesic noramidbpyrine (dipyrone) and the obsolete amidopyrine no longer have any part to play in modern drug therapy in view of the unfavourable ratio of efficacy and adverse effects.* [written in Jan, publ in April]

• Anon. Die arzneimittelinduzierte Agranulozytose. (Drug- induced agranulocytosis). Arzneimittelbrief 1983; 17: 89-92. // Dipyrone is the no. 1 cause of agranulocytosis in South Germany and East Switzerland.

1986 • Anon. GehOrt Metamizol CNovalgin u. A.) zu den 'sichersten Schmerz-mitteln'? (Is dipyrone one of the 'safest analgesics'?) Arznei-telegramm September 1986: 82-83.

• Anon. Metamizol (Novalgin) in der Diskussion (dipyrone under discussion). Arznei-telegramm November 1986: 106"107. '

• Kimbel KH. Arzneimittelsicherheit - wer hat das Sagen? (Drug safetywho has the say?) Deutsches Artzebl1986; 83 (Heft 34/35, 25 Aug): 2275. // Critical commentary apropos the planned dipyrone hearing by the BGA, "the BGA owes it to patients and doctors to take action now".

• Levy I. The saga of dipyrone. Modern Medicine of South Africa, Nov 1986; 52-54. // Distributed by Hoechst. An uncritical report by the journal's editor, who as he states was invited by Hoechst to attend the presentation of the lAAAS at the Clinical Pharmacology Congress in Stockholm.

• Moffatt J. Dipyrone-containing analgesics. South African Med J 1986; 70: 331-3.// Describes hazards of dipyrone which continues to be used in analgesics throughout Africa. 'The continued use of these products is difficult to justify when safer alternatives are available:

• Anon. Dipyrone: hearing by the German drug authority. Lancet 1986; 2: 737.// Reports the Sept 1986 hearing.

Thiele A. Abwehr van Arzneimittelrisiken; Metamizol-haltige Arzneimittel. Bundesgesundheitsamt Pressemitteihmg dated 17.11.86. // Official German press statement on dipyrone .

• Anon. West Germany: Federal Health Office decides on dipyrone. Lancet 1986; 2: 1450-51. // Summarises decision based on Sept 1986 hearing.

1987 • Anon. West Germany: dipyrone put on prescription. Lancet 1987; 1: 95.

• Kewitz H. Metamizol: Flihrt die Indikationseinschrankung zu einem Rlickgang der Agranulozytose? (Dipyrone: Does the restriction of indications lead to a reduction of agranulocytosis?) Deutsches .Arztebl 1987; 84 (Heft *28/29):* A 1972-1978.

• Gross R, Forth W. Das Metamizol-Problem. (The dipyrone problem). Deutsches .Arz~ebI1987; 84 (Heft *28/29)* A 1975-1976. // Editorial on preceding article.

* Rummel W. Metamizol: Kommentar zu Berichten tiber lebensbedrohliche Kreislauferkrankungen. (Dipyrone: commentary on reports of lifethreatening circulatory disorders). Deutsches Arztebl1987; 84 (Heft 50): B-2408-2412. [available in English] // Prepared on behalf of the Medicines Committee of the German Physicians. Summarises existing data, especially on anaphylactic reactions to dipyrone, and on disseminated intravascular coagulation. Tabulates the reports of serious adverse reactions to dipyrone, aspirin and paracetamol between 1970 and 1986: many more were reported with dipyrone than with aspirin and paracetamol.
In a postscript the editor tries to explain how he came to publish such divergent opinions on the hazards of dipyrone (see Kewitz above):

TEXT: *POSTSCRIPT The collaboration between the Medicines Committee of the German Physicians (the Arzneimittelkommission, AMK) - an official committee of the Federal Organisation of Physicians - and the Deutsches Arzteblatt is in the writer's view excellent, and not only because of our close proximity and frequent contact. As part of this we not only publish the official statements, for which we have no editorial responsibility, but also preferentially publish reports which state the opinion of the AMK* or *of its individual members. This remains.so when opinions sometimes differ on the difficult balance between benefit and risk, even though in general the Deutsches Arzteblatt should make up its mind and present one opinion.*

Dipyrone is a good example. We have - with the knowledge of the AMK - published the contribution from the clinical pharmacologist Prof Kewitz (Heft 28/29, *11.*7.87), *as well as the responses to it from readers (Heft 47, 19.11.87), and have at the same time given the executive of the AMK, here represented by Prof Rummel, the opportunity to make their contribution to the dipyrone problem. He focuses especially on shock and disseminated intravascular coagulation, instead of the haematological complications which have received much more attention. Here the pathological mechanisms are in my view even harder to distinguish than with agranulocytosis* (see *e.g. the editorial on the Moschkowitz syndrome, DA. Heft* 44, *29.10.86).*

One must agree with Prof Rummel and the authors he cites that the dipyrone which has until recently been present in many combination products may have sensitised susceptible patients. If it is possible at all, one will not be able to be more precise until all the data from the much-quoted Boston study are available, which they are not today.

In my 40 years' practice of internal medicine I have mostly used an opioid such as levomethadone for seriously ill patients, for example with pre-existing granulocytopenia which was particularly frequent in my clinic, and can recall no complications; but I also cannot recall one with dipyrone (e.g. Novalgin).

The drastic decrease in prescriptions of narcotics after the introduction of the new prescription forms (meanwhile somewhat less!) shows that doctors were not exactly encouraged to use opioids, though it is not disputed that they rarely cause allergic or sensitising effects. To ease this problem, without throwing out the baby with the bath water, would be a rewarding task for the AMK in its present intensified collaborations with the Federal Health Office.

The editorial by the pharmacologist Prof Forth and myself which accompanied Prof Kewitz's contribution in De 28/29 (11.7.87) *was intended to be explanatory and to help readers. It requires no amendment.*

• Glaeske G. Metamizol und Agranulozytose. (Dipyrone and agranulocytosis) Dtsch Apotheker Zeitung 1986; 26 (37): 11 Sept 86.
• Anon. (Buscopan Compositum, a dipyrone-containing preparation, is available in the market again.) Arzte Zeitung 30.11.87.

1988 • Masche UP. AnalgetikalAntipyretika. Pharma-kritik 1988; 10: 37-40.// A Swiss view (in German). Concludes: 'The use of dipyrone *may be* justified in colics or other exceptional cases, but the drug should certainly not be sold without prescription.' (italics added)
• Kiatboonsri P, Richter J. Unethical trials of dipyrone in Thailand. Lancet 1988; 2: 1491.// Criticises 3 trials planned by Hoechst.

The following sections on Case reports, Clinical studies, Materials distributed by Hoechst, and Newspaper reports are very incomplete.

Case reports

• Mintz D, Shaklai M, Pinkhas D. Vries A de. Drug-induced agranulocytosis; a survey of 23 episodes. Rev Roum Med - Med Int 1975; 13: 205-208.
• Zoppi M. Hoigne R. KeUer MF, Streit F, Hess T. BlutaruckabfaU unter Dipyron (Novaminsulfon-Natrium). Ergebnisse aus dem komprehensiven Spital-Drug-Monitoring Bern (Acute hypotension from dipyrone: results form comprehensive drug monitoring in Bern). Schweiz Med Wochenschr 1983; 113: 1768-70. // A systematic analysis of cardiovascular reactions among 2053 patients given intravenous dipyrone. A fall in blood pressure was found in 7 of these, a frequency of 0,34%. In 6 of these 7 patients the blood pressure took longer than 10 hours to recover. In 5 of them the systolic pressure was still below 100 mmHg after 10 hours.
• Zijlmans JM, Claas FHJ, Overbosch D. Baralgin, pain or -penie? (Baralgin, pain or -penia?). Ned Tijdschr Geneesk 1987; 131: 500-501.// One case.
• Vlist GJ van der, Vught AJ van, Donckerwolcke RAMG, Schobben AFAM. Acute nierinsufficientie en hypertensieve encephalopathie na gebruik van Baralgin. (Acute renal failure and hypertensive encephalopathy after use of Baralgin). Ned Tijdschr Geneesk 1987; 131: 1922-23. // One case.

Clinical Studies

• Lehtonen T, Kellokompu I, Permi J, Sarsila O. Intravenous indomethacin (1) in the treatment of severe ureteric colic: a clinical multicentre study with pethidine and metamizol [dipyrone] as the control preparations. Ann Clin Res 1984; 15: 197-199.// I was successful in 59%, Pin 52%, M in 44%.

• Kewitz H. Harter G, Feldmann U, Kreutz G, Nitz M, Unger E. Analgetika bei Nieren- Gallen und BauchkoHk. (Analgesics for renal, biliary and intestinal colic). Z Allg Med 1986; 62: 842-850. // A drug utilization study, also giving doctors' subjective opinions.
• MiralJes R, Cami J, Gutierrez J. Torne J, Garces JM, Badenas JM. Diclofenac versus dipyrone in acute renal colic: a double-blind controlled trial. Eur J Clin Pharmacol1987; 33: 527-28. // Diclofenac was more effective and for longer than dipyrone.

Distributed by Hoechst

• Hoechst. Medication Up-Date: The Relief of Pain. 1986.
• Lubsen J. Pyrazolones and bone marrow depression: Russian roulette or plane crash? Translation from JAMA (Netherlands Edition) 1987; 5: 180-183. (May) // This is a promotional journal send free to Dutch doctors.
• Kewitz H. Comments on translation of his 1987 paper (cited on p. 2), from Deutsches Arzteblatt 1987; 84(25): 11.7.87.
• Brune K. Comments on 1986: Year of (wrong) decisions in the field of analgesics. Translation from Fortschritte del' Medizin 1987; 105: 77-96. (20.2.87).
• Hoechst. Documents to explain data on dipyrone in USA and elsewhere from the beginning until 1988, and the Boston study. Jan 1988.

Newspaper reports

• Shenton .J. Exporting danger to the third world. The Independent 20-10*1987. //* Background piece to a Channel 4 TV programme on 'Medicines in Mexico: North v. South'
•DolI R. Drugs' bad name (letter). The Independent 30.10.1987. // criticises
• Herxheimer A. Restricted usage (letter) The Independent 2.11.1987. // responds
• Anon. German MP blasts Hoechst over Baralgan sales. The Nation, Bangkok. 21.10.87.
• Khanthong T. Hoechst asserts its drug not harmful; claims of side-effects unrealistic, says company. The Nation, Bangkok 22.10.87.
• Ferriman A. Protests as banned drug is tested on children. Observer, London. 1.1.89, p 13.

Key to survey of dipyrone - containing products

Kcy to Countries/Regions:
AF = Africa; BR = Brazil; CA = Caribbean; HK = Hong Kong; IN = India; lD = Indonesia; MX = Mexico; MD = Middle East; PH = Philippines; PK = Pakistan; SA = South Africa; TH = Thailand

Key to other ingredients:

Ad = adipheninc; Ah = aluminium hydroxide; Am = aminopyrine; As = aspirin; Av = avapyrazone; Bd = belladonna; Cc = chloramphenicol; Cf = caffeine; Ch = chlordiazepoxide; Ci = ciclonium; Co = codeine; Cp = chlorpheniramine; Cs = carisoprodol; Cz = chlormezanone; Dc = dicyclomine; De = dexamethasone; Dh = diphenhydramine;
Dm = dimethylaminoacetylphenothiazine; Dx = dextropropoxyphene; Dz = diazepam; Ep = ephedrine;
Er = ergotamine; Eu = eucalyptis; Fv = fenpiverinium; Gu = guaiphenesin; Ha = homatropine;
Hb = hyoscine-n-butylbromide; Hh = hyoscine hydrobromide; Ih = isometheptene; Ld = lidocaine;
Mp = meprobamate; Mr = mepyramine; Or = orphenadrine; Ot = oxytetracycline; Pa = paracetamol;
Pb = phenobarbitone; Pc = procaine; Pd = prednisolone; Ph = phenylbutazone; Pm = promethazine; Pn = penicillin;
Pp = papaverctum; Pr = propyphcnazone; Pt = pitofenone; Pv = pramiverine; Tm = tiemonium methylsulphate;
Uk = unknown; Vi = vitamins

BRAND NAMES OF PRODUCTS CONTAINING DIPYRONE

NO.	BRAND NAME	COUNTRIES AVAILABLE	OTHER INGREDIENTS	COMPANY
1	Acodon	TH		Thai Nakorn
2	Algosfar	MX		Medifarma
3	Aminocid	BR	Vi	Faria
4	Anadex	IN	Dx	Concept
5	Anador	BR	Dh	De Angeli
6	Analgedor	BR	Ha,Pp	Joma
7	Antalgin	ID		Soho
8	Antrain	ID	Ch	New Interbat
9	Apracur	BR	Ep,Vi	Berlinmed
10	Arsinal	ID	Vi	Meprofarm
11	Ascorbgrip	BR	VI	Zulzke
12	Avafortan	IN,SA[1]	Av	Asta Werke
13	Ayoral	MX	Ha,Pp	Rayere
14	Baralgan	AF,CA,IN,ME,SA,TH	Pt,Fv	Hoechst
15	Baralgin	BR	Pt,Fv	Hoechst
16	Baralgina	MX	Pt,Fv	Hoechst
17	Belatropin	BR	Ha,Dz,Pp	Flopen
18	Benodon	ID	Am,Id	Bernofarm
19	Beserol	BR,ID,MX	Cz	Winthrop
20	Bestopyron	ID	VI	Tanabe
21	Biovulmin C	BR	Mr,Vi	Apsen
22	Bipasmin Camp.	BR,MX2	Uk	De Angeli
23	Blisspyron	PK		Bliss
24	Bridanol	MX		Promeco
25	Bromalgina	BR	Ha,Co	Climax
26	Bromalgina	BR	Ha,Co	Climax
27	Broncopinol	BR	Eu,Vi	Luper
28	Busconet	MX	Hb	Quimica Sons
29	Buscopan Camp.	BR,MX,SA	Hb	Boehringer Ing.
30	Butilamina Comp.	MX	Hb	Ehlinger
31	Byladoce Dp	MX	Vi	Sanofi
32	Calmetron	MX	Pp	Index
33	Calmona	BR		Prima
34	Calmona	BR	Pa,Cf	Prima
35	Cariflex	PK	CS,Cf	Opal
36	Cennoval	ID		Japhar
37	Cetalgin	ID	Ch,Dx,Cf,Vi	Soho
38	Cetalgin-T	ID	Cf,Vi	Soho
39	Cintaverin Camp.	MX	Pv	E.Merck
40	Colepren	MX	Hb	Farmaquila
41	Conmel	AF,BR,ID,MX,ME,TH		Winthrop
42	Cortagrip	BR	EU,VI	UCI-Farma
43	Cybamate	TH	Mp	General Drugs Hse
44	Cymamidon	ID	Id	Imedco F.
45	Dactron	ID	Ch,Cf,Vi	Kenrose
46	Dalgex	BR	Pp	Farmoquimica
47	Dalmasin	MX		Columbia
48	Danalgin	ID	Ch,Cf,VI	Dankos
49	Debela	SR		Srasifa
50	Della-Benabion	ID	Vi	Dupa
51	Deparon	ID,TH3	Mp	Westmont
52	Dexalgen	SR	Vi	De Angeli
53	Diarona Inj.	SR	Ha,Pp	Honorterapica
54	Diarona Sol.	SR	Ha,Pp	Honorterapica
55	Dia-Fastalgin	ID	Dz	Pharos
56	Dilubrin	SR	Uk	UCI-Farma
57	Dipirol	SR	Ha,Pp	Royton
58	Dipirona	SR		Biochimica
59	Dipirona	SR		Faria
60	Dipirona	SR		Flopen
61	Dipirona	SR		lab Farma.

NO.	BRAND NAME	COUNTRIES AVAILABLE	OTHER INGREDIENTS	COMPANY
62	Dipirona	BR		Legrand
63	Dipirona	BR		Luper
64	Dipirona	BR		Natus
65	Dipirona	SR		Qulmloterapia
66	Dipirona	BR		Q.J.F.
67	Dipirona	BR		Royton
68	Dipirona	BR		Sedabel
69	Diplrona W.	BR	Eu	Windson
70	Dipirone	BR		Laborsil
71	Dipirone	BR		Mesquita
72	Dipromate	TH	Mp	Asian Pharm
73	Dipyron	PK		Efroz
74	Dipyron	PK		Eiffel
75	Dipyron	PK		EPLA
76	Dipyron	PK		Eros
77	Dipyron	PK		Fazul E.
78	Dipyron	PK		Geofman
79	Dipyron	PK		Hakimsons
80	Dipyron	PK		LC & PW
81	Dipyron	PK		Lisko
82	Dipyron	PK		Mendoza
83	Dipyron	PK		Polfa
84	Dipyron	PK		Reko
85	Dipyron	PK		Unesko
86	Dipyron Sodium	PK		Pliva
87	Di-Tral	MX	Cp	Berman
88	Dolnefort	MX	Vi	Farcoral
89	Dolo Neurobion	ID,MX	Vi	E.Merck
90	Dolo Neurobion F.	MX	Vi	E.Merck
91	Dolo Scanneuron	ID	Vi	Scanchemie
92	Doloradin	ID	Vi	Bernofarm
93	Dolo-Adamon	AFR,ME.TH4	Ci	Asta Werke
94	Dolo-Nervit	TH	Vi	Greater P.
95	Dolo-Pangavit	MX	Vi	Wallace
96	Dolo-Tiaminal	MX	Vi	Silanes
97	Dora/gin	BR	Hh	Dorsay
98	Dorten	BR	Or,Ha	Calbos
99	Dortlex	BR	Or,Cf	Merrell
100	Daril P	BR		Dorsay
101	Darlisin	BR	Pm	Rorer
102	Darostil	BR	Ha,Pp	Medic
103	Darscopena	BR	Uk	Ariston
104	Dysminal	ID	AS,Cf,Pb,Hb	Otto
105	Escapin	MX	Hb	Streger
106	Espasmobel	BR	Ha,Pp	Opofarm
107	Espasmo-Qual	MX	Dc.Dx	Silanes
108	Eucaliptol Compo	BR	Eu,Vi	Mesquita
109	Everalgin	BR		Eversil
110	Exodalina	MX		Quimica Sons
111	Falgin	ID	Cf,Ch,Vi	Prafa
112	Farlin	MX		Continentales
113	Farlin 2	MX		Continentales
114	Farlin 500	MX		Continentales
115	Farodalina	MX		Continentales
116	Farodalina Compo	MX	Dx	. Continentales
117	Fastalgin	ID		Pharos
118	Fastan	ID		New Interbat
119	Febralgjn	BR		De Angeli
120	Flenalgin	BR	Uk	Fleming
121	Fluviral	BR	Mr,Cf,Vi	Searle
122	Frenopulmin C	SR	Eu,Vi	Zambeletti
123	Gardan	PH	Pa	Winthrop
124	Genergin	TH		General Drugs Hse

NO.	BRAND NAME	COUNTRIES AVAILABLE	OTHER INGREDIENTS	COMPANY
125	Gifaril	PH		Sandoz
126	Gripefago	BR	Mr,Cf	Majer Meyer
127	Grlpion	BR	Dh,Vi	Makros
128	Gripol Bals.	BR	Eu,Vi	Quimioterapia
129	Grlpol Compo	BR	Mr,Cf,Vi	Quimloterapia
130	Grlpomatine	BR	Eu	Q.I.F.
131	Guacocilina	BR	EU,Pc.Pn	Sanus
132	Hifluton	ID	Pb,Cp,Bd,Pr.Cf	Himajaya
133	Himagen	ID	Ch	Himajaya
134	Inatrex Bais.	BR	EU,Ot	Inaf
135	Inatrex Compo	SR	EU,Ot,Gc	Inaf
136	Indigon	MX		IQFASA
137	Intermidon X	ID	Am,Ld	New Interbat
138	Interneural	ID	Ch,Cf,Vi	New Interbat
139	Invogin	TH		Chew Bros.
140	Kal pyron	ID		Kalbe Farma
141	Kiligrip	BR	Gu,Vi	Sedabel
142	Kindpasm	BR	Ha,Dz,Pp	Kinder
143	Kno-Paine	TH		Continental
144	Lagalgin	CA,PH		Lagap
145	Lisador	SR	Ad,Pm	Farmasa
146	Maderil	MX		Marcel
147	Magnol Atlantis	MX		Atlantis
148	Magnolasa	MX		Atlantis
149	Magnopyrol	SR MX~ PK[6]		Abbott
150	Mecoten	MX	Pp	Promeco
151	Medalgin	TH		Medical Sup.
152	Melpen	BR		Flopen
153	Melubrin	PH		Hoechst
154	Mepron	ID		Meprofarm
155	Mepronal	ID	Ch	Meprofarm
156	Meta Sioneuron	ID	Vi	Phapros
157	Metamizol	PK		Opal
158	Metamizol	PK		Sibro
159	Metamizol	BR		Veafarm
160	Metamizol V.	BR		Veafarm
161	Metaneuron	ID	Ch,Dz.Cf,Vi	Phapros
162	Metilon	HK,ID,TH		Daiichi·
163	Migrane	BR	Er,Cf	Novaquimica
164	Mio Nervix	SR	CS,Vi	Novateraplca
165	Mio-Citalgan	SR	CS,Cf,Vi	E.Merck
166	Nalgin-P	TH		PP Lab
167	Nebagin	AF,ME		Ipca
168	Neomed	ID		Kenrose
169	Neonovapyron	ID		Ethlca
170	Neosaldina	BR	Ih,Cf	Knoll
171	Neo-Melubrina	MX		Hoechst
172	Neo-Protal	ID	DZ,Cf	Pharmac A.
173	Neuralgin	ID	Cf,Vi	Kalbe Farma
174	Neuralmon	BR	Pb	Laborsil
175	Neuribel	BR	Vi	Riedel
176	Neurobiovit +	ID	Vi	Prafa
177	Neurodial	ID	Ch,Vi,Cf	Klmia Farma
178	Neurogen	ID	Ch,Vi	Bernofarm
179	Neurogesic	ID	Ch,Dz,Cf,Vi	Abdi
180	Nevralgex	BR	Or,Cf	Honorterapic
181	Nevralgina	BR		Climax
182.	Nominbar	HK	Mp	Atlantic
183	Nominfone	TH		Atlantic
184	Norpain	TH	Dx	Bessy Aron
185	Novalgin	AF,CA,HK,IN,ID,ME,PK,TH		Hoechst
186	Novalgina	BR		Hoechst
187	Novaminsulfon	HK		Waldemar

NO.	BRAND NAME	COUNTRIES AVAILABLE	OTHER INGREDIENTS	COMPANY
188	Novapam	TH	Pa	Asian Pharm
189	Novazolon	BR	De.Pd	Hobson
190	Novopyrin	PK		Specific
191	Novoquinol C	BR	Mr	Legrand
192	Olangln	TH		Olan
193	Olangin/Lidoc.	TH	Ld	Olan
194	Oxigricol	MX	Ld.Ot	Rimsa
195	Pamagin	IN	Oz	Alkem
196	Panstop T	ID	Ch	Conmed
197	Par	BR	Pa	Sanof!
198	Pifrol	MX		Arlex
199	Pinusan	BR	Eu.Vi	Laborsll
200	Piraken	MX		Kendrick
201	Pirongyl	MX		Arlex
202	Plenocedan	BR	Ha.Pp	Makros
203	Procolic	ID	Hb	Meprofarm
204	Prodolina	MX		Promeco
205	Promalgin	IN	Pa.Cf	Uniloids
206	Proneuron	ID	Oz.Cf,VI	Meprofarm
207	Pulmonutrol	BR	Eu.Vi	Flopen
208	Pulmoquim	BR	Eu.Vi	1.0. Camplnas
209	Pyralgln	TH		Siegfried
210	Pyronal	ID		Tanabe
211	Rapldon	ID		Mecosin
212	Rheuvitine	BR		Medic
213	Ridol	ME	Ha,Om,Co	Medimpex
214	Roanalgin	ID		Oexa Medica
215	Rumalisine	MX	Ph.Ah,Vi	Briter
216	Scanalgin	ID		Scanchemie
217	Sedabel	BR		Sedabel
218	Sedabrine	BR		Legrand
219	Sedalene	BR		Gunther
220	Sedyn-A Forte	IN	Dh.Oz	MM Labs
221	Selpiran	MX	Hb	Diba
222	Sinvirol	MX	Uk,Vi	Infan
223	Siplrin	TH		SiamB.
224	Somaflex	BR		Novaquimica
225	Spasmizol	IN	Ha,Pb	10PL
226	Spasmotropin	BR		Legrand
227	Stileran	ID	Ch.Cf,Vi	Combiphar
228	Sulpyrin	TH		China Chem.
229	Supranal	ID	Cf,Vi	Oexa Medica
230	Tebasedan	BR	Ha.Pp	Windson
231	T ermavit	BR	Vi	Exp. Cientifica
232	Tetrapulmo	BR	Cp	Hobson
233	Toloxin	BR		Searle
234	Totalgin-C	BR	Vi	Odontomed
235	Trlnalgen	BR	VI	Oe Angeli
236	Ultragin	IN	Pa.Cf	Manners
237	Unagen/AMR	ID	Ch	United Amer.
238	Unigin	TH		Unison
239	Utidol	MX		Oiba
240	Verabeum	BR	Ha.Pp	Zulzke
241	Visceralgin +	ID	Tm	Organon
242	Xylomidon	ID	Am.Ld	Dupa
243	Zimalgin-A	IN	Pa.Co.Cf	Rallis
244	Zolidin	MX		Kener

Notes:

1. Marketed by Noristan in South Africa; 2. Marketed by Promeco in Mexico; 3. Excludes Mp in Thailand;
4. Marketed by Schcring AG ill Thailand; 5. Marketed by Sigfried in Mexico; 6. Marketed by Sigfried in Pakistan