

**Rapporteur's
Public Paediatric Assessment Report
for paediatric studies submitted in accordance
with Article 45 of Regulation (EC) No 1901/2006, as
amended**

Voltaren and generic products

Diclofenac

DE/W/001/pdWS/001

Rapporteur:	Germany
Finalisation of procedure	27th September 2010
Date of finalisation of PAR	27th September 2010

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	Voltaren and generic products
INN (or common name) of the active substance(s):	Diclofenac sodium Diclofenac potassium Diclofenac resinate Topical diclofenac diethylamine
MAH (s):	Novartis
Pharmaco-therapeutic group (ATC Code):	M01AB05, M02AA15
Pharmaceutical form(s) and strength(s):	See Section IV

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List of abbreviations

ADR	adverse drug reaction
AE	adverse events
AUC	area under the curve of blood/plasma concentration versus time
ALT	alanine transaminase
ALP	alkaline phosphatase
AST	aspartate transaminase
BA	bioavailability
BSA	body surface area
BCS	Bio-pharmaceutics Classification System
BW	body weight
CDS	Core Data Sheet
CHEOPS	Children's Hospital of Eastern Ontario Pain Scale
CL	clearance
C _i /F	oral clearance
C _{max}	maximum blood/plasma concentration
CV	coefficient of variation
DEA	diethylamine
EC	European Commission
ECT	enteric coated tablets
d	day
DMARD	disease modifying anti-rheumatic drug
ENT	ear, nose or throat
EU	European Union
F	female
FDA	Food and Drug Administration (US Health Authority)
GI	gastrointestinal system
h	hour
HLT	MedDRA High Level Term
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
i.m.	intramuscular administration
IMS	IMS Health database
i.v.	intravenous administration
JIA	juvenile idiopathic arthritis
JRA	juvenile rheumatoid arthritis
K _d	dissociation constant
LPD	The Cegedim Longitudinal Patient Database
M	male
MA	marketing authorisation
MAH	Marketing Authorisation Holder
MS	Member State
NA	not applicable
NHANES	National Health and Nutrition Examination Survey database
NONMEM	Non linear Mixed Effect Modeling software
NSAID	non-steroidal anti-inflammatory drug
n	number of subjects in study/treatment group
OPS	objective pain scale
OTC	over the counter / non-prescription medicines
peri-OP	peri-operative
post-OP	post-operative
PK	pharmacokinetics
PMS	post-marketing surveillance

p.o.	per os (oral) administration
POM	prescription only medicines
PONV	post-OP nausea and vomiting
POP	post-operative and post-traumatic pain
PUMA	paediatric-use marketing authorisation
PRR	proportional reporting ratio
PT	MedDRA Preferred Terms
RCT	randomized controlled trial
SD	standard deviation
SIGN	Scottish Intercollegiate Guidelines Network
SMQ	Standard MedDRA Query
SmPC	Summary of the Products Characteristics
SOC	MedDRA System Organ Class
SSTC	Skin and Soft Tissue Complications
ST	sulfotransferase
T1/2	Half life
THIN	The Health Improvement Network Database
Tmax	time of maximum blood/plasma concentration
t.i.d.	ter in die / three times a day
UK	United Kingdom
UGT	glucuronosyltransferase
VAS	visual analogue scale
VDS	verbal descriptor scale
Vd	Volume of distribution
WT	weight
yr	year

I. EXECUTIVE SUMMARY

Introduction

Systemic formulations

Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) in use for over 30 years for the treatment of anti-inflammatory and painful conditions. It is available in several galenic formulations employing sodium salt (Voltaren), potassium salt (Cataflam – POM or Voltaren - OTC), free acid or a combination with colestyramine (“diclofenac resinate”), where diclofenac is bound on resinate as an ion exchanger.

According to the CDS of the MAH Novartis, diclofenac is recommended for use in paediatric patients as a prescription only medicine (POM) in acute conditions such as post-traumatic, postoperative pain, inflammations and swelling, and severe painful inflammatory infections of the ear, nose or throat (as an adjuvant therapy), as well as in a chronic indication such as juvenile rheumatoid arthritis. Lower doses (up to 75 mg/day) of diclofenac are also available over-the-counter (OTC) in adolescents of 14 years of age and over for the treatment of headache, dental pain, primary dysmenorrhoea (period pain), rheumatic pain, muscular pain and backache, relief of symptoms of colds and flu, including aches and pains and sore throat and reduction of fever.

The data package, primarily submitted by one MAH (Novartis) under article 45 of the Paediatric Regulation, comprises preclinical studies in juvenile animals and clinical studies conducted in children and adolescents, together with non-clinical and clinical overview reports. The MAH also summarised the spontaneous suspected adverse event reports which have been received by the Company relating to use in children. The responses of the MAH to the LoQ (PrAR 17th March 2009) comprise efficacy and safety data allocated to the 3 claimed indications of the systemic application: “acute postoperative pain” (POP), “pain and fever related to infections of the ear, nose or throat” (ENT) and “juvenile idiopathic arthritis” (JIA).

Topical formulations

Diclofenac diethylamine (INN: Diclofenac diethylammonium salt) is a non steroidal anti-inflammatory drug (NSAID) designed for topical application (ATC code M02A A “Topical products for joint and muscular pain. Anti-inflammatory preparations, non-steroids for topical use”).

Diclofenac diethylamine is recommended for the relief of pain and inflammation due to soft-tissue injuries, soft-tissue rheumatism and localised arthritic conditions in adults and in adolescents aged 12 years and over.

The data package, primarily submitted by one MAH (Novartis) under article 45 of the Paediatric Regulation, comprises pharmacokinetic data and some data from clinical studies, mainly conducted in adults. The MAH also summarised the spontaneous suspected adverse event reports which have been received by the Company relating to use in children. The response of the MAH to the LoQ (PrAR, 17th March 2009) comprises mainly pharmacokinetic and safety data for the topical application.

There is no uniformly justified paediatric posology for diclofenac-containing topical products in the approved SmPCs in EU countries.

Development of procedure

Following receipt of the Novartis response to the diclofenac Article 45 (Day 70) Draft Assessment Report on November 9th, 2009, BfArM (Rapporteur) issued its Day 90 Preliminary Assessment Report. Four member states (SE, NL, FR, UK) subsequently provided comments by Day 115 of the work-sharing assessment procedure. SE agreed with the Rapporteur and had no further comments. NL, FR and UK provided detailed comments to the PrAR. On June 1st, 2010 the Rapporteur shared the concerned Members States comments together with the Rapporteur's responses with Novartis, giving the applicant an additional one month clock-stop to address the remaining outstanding issues. Subsequently BfArM gave Novartis further opportunity for discussion: Novartis comments (30th June 2010), response by BfArM (12th July 2010), Novartis comments (2nd August 2010), Rapporteurs responses (5th August 2010), TC on 9th August 2010), final comments Novartis (16th August 2010).

Summary of conclusions

Systemic formulations

After assessment of the MS comments received and extensive discussion with the MAH a revised posology for the oral solution, tablets and suppositories for the acute indications for systemic application is agreed.

Based on the current divergent opinions across member states, a full harmonization of paediatric relevant parts of the product information for diclofenac for children with regard to the chronic indication juvenile idiopathic arthritis (JIA) apparently cannot be achieved during this work sharing procedure. Further to the circulation of the Rapporteur's Day 90 PrAR, three MS did not agree with the position of the Rapporteur that efficacy and safety of diclofenac in the indication JIA has not been sufficiently documented in controlled clinical studies. The Rapporteur maintains his opinion.

The Rapporteur recommends implementation of a wording for the revised indications and posology in MSs via type IB variation. However, it is acknowledged that three MS are not in agreement (indication JIA) and that in this MS it may be appropriate to retain the product Information which is currently authorized or to implement only parts of the recommendation.

Topical formulations

After assessment of the MS comments received and extensive discussion with the MAH Novartis, a general age limitation for use of topical diclofenac in children below 14 years for flexible dosed topical formulations and below 16 years for fixed dosed topical formulations like plasters is recommended. Furthermore, a use as short-term treatment for children and adolescents is recommended by the Rapporteur.

On basis of the limited data available for children for the topical application of diclofenac, only the acute pain indication is recommended by the Rapporteur for this age group.

The Rapporteur recommends implementation of a wording for the revised indications and posology in the member states via type IB variation. However, based on the current divergent licensed indications in the member states and the divergent opinion of the MAH, the full harmonization of paediatric relevant parts of the product information for topical diclofenac for children and adolescents apparently cannot be achieved and for some member states it may be appropriate to retain the product information which is currently authorized or to implement only parts of the recommendation.

Ophthalmological formulations

The diclofenac-containing eye drops Voltaren ophtha und Voltaren ophtha sine are only licensed for use by adults. There is no need in the paediatric population. This is also recommended and justified by the Rapporteur (see PrAR 17th March 2009). No further discussion is considered necessary with regard to the ophthalmological indication therefore no further information is included in this AR.

II. RECOMMENDATION

After evaluation of the presented data and of the comments received from MSs and Novartis, the Rapporteur is of the opinion that not all paediatric indications claimed in the CDS are in accordance with the scientific basis and the need in children. The MAH has agreed to a revised posology for acute indications, which is welcomed.

In order to achieve a justified update and improvement of the available pharmaceutical formulations and an evidence-based posology for a treatment with diclofenac-containing products in children, the following measures are recommended (see below):

In general, the Rapporteur recommends an implementation of the wording for the revised indications and posology in MS via type IB variation.

II.1 Systemic application

II.1.1 Indications 'acute post-operative pain after minor surgery' (POP) and 'pain and fever related to infections of the ear, nose or throat (ENT), e.g. pharyngotonsillitis, otitis'

Rapporteur's position

Overall the data are considered sufficient to support the use of suppositories and tablets of strength 12.5 mg and 25 mg for the indication 'short-term treatment of acute post-operative pain after minor surgery' and 'pain and fever related to infections of the ear, nose or throat (ENT), e.g. pharyngotonsillitis, otitis' in children of different age with a weight-related daily dose of 2 mg/kg. Only pain relief in minor surgery is shown in the presented studies. Therefore, in the opinion of the Rapporteur, this issue should be reflected in the wording of the indication.

Overall the data are considered sufficient to support a recommendation for 1.5 % diclofenac oral solution (diclofenac resinat drops) for the indication short-term treatment of POP and ENT in children of age 1 – 5 years with a weight-related daily dose of 1.5 mg/kg. For children under the age of 1 year, no separate data are available. The 1.5 % diclofenac oral solution is considered not therapeutically appropriate for use in children above 5 years of age because that would require a dosing of more than 140 drops per day.

The data presented for POP could be extrapolated to the indication ENT. It is therefore endorsed to give a joint dose recommendation for both acute indications ENT and POP. There are marketing authorisations for both indications in EU countries for children >14 years, concerning diclofenac potassium, and >1 year, concerning diclofenac sodium.

As the proven frequency of the adult dose recommendation is 3 times daily for immediate release formulations, it is assumed that this will warrant also for children the best maintenance of pain relief with the best safety profile.

The 50 mg tablet is considered not appropriate for use in children. The single dose for adults in acute pain is 12.5 – 50 mg diclofenac with a maximum of 75 mg per day. However, the 50

mg tablet when given three times daily exceeds the appropriate maximum daily dose in children >12 years. The suppositories have a comparatively high C_{max}, insofar there could be an increased risk related with the 50 mg single dose. 150 mg daily is a proven dose for the treatment of rheumatic diseases in adults.

In general (also for the 25 mg strength), gastro-resistant formulations may be not therapeutically adequate for a treatment of acute conditions because of their known delayed onset of efficacy.

The doses (weight related daily dose of 1.5 mg/kg for oral solution and 2 mg/kg for suppositories and tablets) for the acute indications POP and ENT as recommended by the Rapporteur, taking into consideration MS and Novartis comments, are summarised in the table below (see under conclusion).

Summary of comments received from MSs

NL comment: In the indication pain and fever-related infections, the Rapporteur does not recommend 25 mg tablets in children aged 9-11 years and 12-16 years.

There is no reason why 25 mg tablets can not be effective in these 2 older age groups.

The Rapporteur's justification is that the studies were done only for a few days. However, based on clinical experience there is no reason why the use of diclofenac should be limited to a few days if the patient is being benefited. Instead, it is recommended to mention that treatment should be limited to the duration of pain and fever.

Furthermore, there is no logical explanation why children younger than 12 years should have a shorter treatment period in comparison to the older age group.

In the indication acute post-operative pain after minor surgery, the Rapporteur does not recommend drops 1.5% in patients aged 1-5 years.

Contrarily, the NL-Assessor considers this acceptable. There is no reason why drops 1.5% can work in pain and fever-related infections but not in post-operative pain.

UK comment: In the indication pain and fever-related infections, the UK agrees with the Netherlands that 25 mg tablets should be indicated in children aged 9-11 years and 12-16 years.

We agree with the Rapporteur that the duration of treatment should be only for short term use i.e. a few days (as in the UK SmPC for ibuprofen syrup).

For the indication acute post-operative pain after minor surgery, the UK agrees with the Netherlands that the 1.5% drops should be indicated in patients aged 1-5 years.

FR comment: It should be noted that the weight related daily doses of 2 mg/kg for these acute indications (POP, ENT) are in the range of the daily dose usually recommended in France for systemic diclofenac containing medicinal products.

The proposed limitations of treatment duration (7 days / 14 days) are not endorsed. France considers that statement issued from the PhWVP "Keys Elements" procedure adopted by the CHMP in October 2005 (*Undesirable effects may be minimised by using the minimum effective dose for the shortest duration necessary to control symptoms*) could be sufficient.

France has no comment on the proposed acute indications (post operative pain, pain and fever related to infections of ENT) as they are not nationally granted.

Summary of comments received from Novartis

Novartis agrees with the position of the UK that the duration of treatment should be only for short term use.

There is agreement on the wording for short term, symptomatic treatment of pain related to inflammatory infections of the ear, nose or throat (ENT).

While acknowledging the limitation of the submitted clinical trial data in children, the positive benefit risk of diclofenac in the treatment of both post-operative and post-traumatic pain is well established worldwide in the adult patient population by controlled clinical trials. Although Novartis maintains its opinion regarding paediatric posology of tablets and suppositories 25 and 50 mg, Novartis respects BfArM's recommendation in this area. Under consideration of the divergent opinions of some member states and BfArM it may be a relevant and pragmatic solution to implement only some parts of the proposed harmonised paediatric posology, to maintain the nationally approved age limit for paediatric use or to retain the Product Information which is currently authorised in that particular Member State. With regard to the i.v. and i.m application in children Novartis welcomes the Rapporteur's recommendation, which is in line with the current Company Core Data Sheet. With regard to the use of tablets 75/100 mg in children Novartis welcomes Rapporteur's recommendation, which is in line with the current Company Core Data Sheet.

Conclusion

On basis of the revised data submitted by Novartis the treatment of children with systemic diclofenac can be recommended for the acute indications POP and ENT as short-term treatment for specific formulations and strengths with a revised, joint posology.

Dose recommendations for prescription-only acute indications

The following dose recommendations are agreed (MS, Novartis) for POP and ENT indications and recommended by the Rapporteur:

Oral Drops (1.5%):

Children aged 1 - 5 years (min. 10 kg BW or over) should be given up to 1.5 mg/kg body weight per day in 3 divided doses, depending on the severity of the disorder.

Suppositories (12.5 mg):

Children aged 2 years (min. 13 kg BW) or over should be given up to 2 mg/kg body weight per day in 3 divided doses, depending on the severity of the disorder.

Tablets (25 mg), suppositories (25 mg):

Children aged 9 years (min. 35 kg BW) or over and adolescents should be given up to 2 mg/kg body weight per day in 3 divided doses, depending on the severity of the disorder.

Table: Dose recommendations for acute indications POP and ENT

Body weight (kg) (corres-ponding age)	Dosage forms	Single dose in number of drops, tablets, suppositories (corresponding diclofenac dose)	Maximum daily dose in number of dosage units (drops/tablets/ suppositories)
10-19 kg (1-5 yr)	Drops 1.5%	10 – 20 drops (5–10 mg)	30 – 60 drops (in 3 divided doses)
13-19 kg (2 - 5 yr)	12.5 mg supp	12.5 mg	12.5 mg bid - 12.5 mg tid
20-44 kg (6-11 yr)	12.5 mg supp	12.5 mg	12.5 mg tid
35-44 kg (9-11 yr)	25 mg supp/tab	25 mg	25 mg tid
45-55 kg (12-16 yr)	25 mg supp/tab	25 mg	25 mg tid – 25 mg four times daily

Solution for injection:

With regard to the i.v. and i.m application a use in children and adolescents is not recommended by the Rapporteur which is in line with the current Company Core Data Sheet.

Tablets 75/100 mg:

With regard to tablets 75/100 mg a use in children and adolescents is not recommended by the Rapporteur which is in line with the current Company Core Data Sheet.

Tablets/suppositories 50 mg:

With regard to tablets/suppositories 50 mg a use in children and adolescents is not recommended by the Rapporteur which is respected by Novartis.

Wording of acute indications (prescription-only)

The following wording is agreed (MS, Novartis) and recommended by the Rapporteur:

Symptomatic, short-term treatment (children and adolescents) of

- pain related to inflammatory infections of the ear, nose or throat, e.g. pharyngotonsillitis, otitis (ENT). In keeping with general therapeutic principles, the underlying disease should be treated with anti-infective basic therapy, as therapeutically appropriate. Fever alone without inflammatory component is not an indication.

The following wording is agreed by the MS and recommended by the Rapporteur:

Symptomatic, short-term treatment (children and adolescents) of

- acute post-operative pain after minor surgery (POP).

However, this latter indication is not fully agreed by Novartis. According to Novartis “post-traumatic pain, inflammation and swelling” should be maintained as additional sub-indications, which is not supported by the Rapporteur since data from clinical trials in children are not available for these sub-indications.

Based on the current divergent opinions of the Rapporteur and the MAH concerning the sub-indications “treatment of post-traumatic pain, anti-inflammatory effects and improvement of swelling”, a full harmonization of paediatric relevant parts of the product information for diclofenac for children for this aspect apparently cannot be achieved.

II.1.2 JRA/JIA indication

Rapporteur’s position

The 25/50 mg enteric coated tablets and the 12.5, 25, 50, and 100 mg suppositories have marketing authorizations for JIA (JRA) in some European countries.

However, in the opinion of the Rapporteur, the published evidence for a chronic treatment of JIA with diclofenac is at present considered not sufficient for a justified dose recommendation in children. Relevant information, as requested by the currently valid CHMP-guidelines (CPMP/EWP/556/95, CPMP/EWP/422/04), concerning a weight- and children’s age-related dose recommendation and, in particular, concerning long-term-treatment with diclofenac, could not be obtained from the submitted trials. On basis of the submitted post-marketing experience data there is concern that in particular long-term treatment with diclofenac in children could be related with an increased frequency of hepatic adverse events.

In total, there are only data for 67 diclofenac-treated children available from controlled, double-blind, randomised trials. Differentiated data for single doses, frequency of application and total weight-related daily doses are lacking. On basis of this data, an evaluation of the appropriate dose and a definition of a valid dose recommendation is considered problematic and an unnecessary overtreatment cannot be excluded.

The children included in the mentioned studies were treated for 2 - 4 weeks. Long-term data beyond this treatment duration in order to elucidate the safety profile over time in children are scarce. The only data for long-term treatment may be obtained from one active controlled study where it is questionable how many of the initially 31 patients remained on treatment up to the final study duration of 8 years. However, In particular for long-term-treatment it is necessary to use a proven optimal dose in order to avoid unnecessary dose-related adverse effects.

In conclusion, the Rapporteur is of the opinion that at present the clinical data base is too small for a positive general treatment recommendation for diclofenac in JIA.

Summary of comments received from MS:

The UK raises a major objection to the deletion of the indication for juvenile systemic arthritis, especially for the tablet formulations, since use of diclofenac is established practice in the UK

FR does not endorse the recommendations made by the Rapporteur because diclofenac products are authorised in France for paediatric rheumatic inflammatory diseases including JIA.

NL does not endorse the recommendations made by the Rapporteur because the data of the double-blind, placebo and active-controlled study with diclofenac enteric coated tablets (Haapasaari et al., 1983) are considered sufficient to support the JIA indication in children, although the statistically significant results are based on a low sample size.

SE endorsed the recommendation of the Rapporteur.

Conclusions

Based on the current divergent opinions across member states for the JIA indication, a full harmonization of paediatric relevant parts of the product information for diclofenac for children apparently cannot be achieved concerning this issue

Further to the circulation of the Rapporteur's PrAR, three MS were of the opinion that the JIA indication JIA and the posology currently recommended by the MAH should be maintained, while the Rapporteur is of the opinion that additional clinical data are required for a definition of the optimal diclofenac dose and a characterization of the long-term safety profile of diclofenac in this indication.

The MAH acknowledges the suggestion of the Rapporteur to conduct a long-term observational study in patients with JIA, however, has not provided specific comments on this aspect during the article 45 procedure, as requests for further studies are understood to be out of the scope of the article 45 procedure. The MAH intends to seek clarification and provide further thoughts on this issue post-procedure.

Changes in SmPC wording

The MAH agreed to revise SmPC section 5.1 by including clinical data available for diclofenac use in treatment of JIA as follows:

There is limited clinical trial experience of the use of diclofenac in JRA/JIA paediatric patients. In a randomised, double-blind, 2-week, parallel group study in children aged 3-15 years with JRA/JIA, the efficacy and safety of daily 2-3 mg/kg BW diclofenac was compared with acetylsalicylic acid (ASS, 50-100 mg/kg BW/d) and placebo - 15 patients in each group. In the global evaluation, 11 of 15 diclofenac patients, 6 of 12 aspirin and 4 of 15 placebo patients showed improvement with the difference being statistically significant ($p < 0.05$). The number of tender joints decreased with diclofenac and ASS but increased with placebo. In a second randomised, double-blind, 6-week, parallel group study in children aged 4-15 years with JRA/JIA, the efficacy of diclofenac (daily dose 2-3 mg/kg BW, n=22) was comparable with that of indomethacin (daily dose 2-3 mg/kg BW, n=23).

II.1.3 Safety Issues from post-marketing data

Overall the adverse events reported for post marketing experience with systemic diclofenac in children and adolescents do not relevantly differ from those known for a therapy in adults. No completely new safety issues were identified.

Severe AEs most frequently reported were anaphylactic reactions/anaphylactic shock, liver related disorders (such as hepatic failure, hepatitis, jaundice), gastrointestinal ulcer/perforations, Stevens-Johnson syndrome, Reye's syndrome and agranulocytosis.

On basis of the available case reports, liver disorders including severe ones appear to occur relatively more frequently after >6 month diclofenac treatment in children >12 years than in adults. The reported relative frequencies for jaundice and hepatic function disorder seem to be increased in children compared to adults (2.6% of reported ADR versus 0.9%). In addition, increased plasma levels of marker enzymes for liver damage such as ALT (3.6% versus 1.7%) and AST (3.4% versus 1.1%) were reported more frequently in children than in adults.

In addition, hypothermia appears to occur more frequently in context with diclofenac application in children <6 years than in adults (5% versus 0.3% of total number of ADR reported).

The incidence of accidental intake of diclofenac was particularly high in the group of children <6 years, with a frequency of approx. 30%.

Conclusions

Concerning the addition of a warning regarding an increased risk for accidental intake of topical and systemic diclofenac formulations by children, the Rapporteur intends to take up this issue in the currently ongoing diclofenac PSUR worksharing procedure.

II.1.4 Pharmacokinetic data

With regard to the PK data and the PK related dose-recommendations provided by Novartis, it is referred to the PRAR. In this respect, no further data or comments have been received.

II.2 Topical application

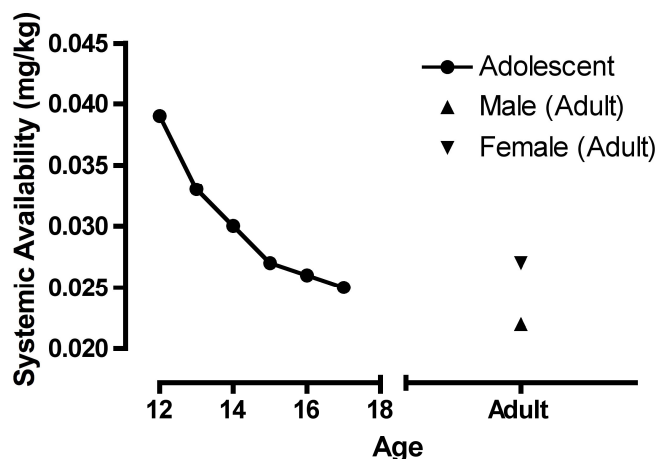
For the topical application of diclofenac in children only scarce evidence concerning efficacy and safety is available from controlled clinical trials.

The nationally licensed products have different age limitations, ranging from use in children >6 years to use in adults only.

- France – the POM license is for adults only. The OTC license is > 15 years.
- Belgium, Greece, Ireland, Italy: no dosage recommendation established for children and adolescents.
- Sweden > 16 years
- Norway > 18 years

Most frequently, the topical use of diclofenac in children of an age below 12 years is not recommended or topical use of diclofenac in children and adolescents is completely contraindicated or no dosage recommendations have been established for them.

Between the age of 12 and 18 years the systemic availability of topical diclofenac decreases and approaches the values known for adults (see figure below).



The MedDRA SOC AEs age related distribution is suggestive of a relative increase in systemic versus topical AEs in the group of adolescents (>12 years – 18 years) in comparison to adults. Whereas in both groups the proportion of skin adverse events (31.4% versus 37.5%) is comparable, the relative proportion of gastrointestinal disorders (15.7%

versus 7.8%), injury, poisoning and procedural complications (11.8% versus 4.0%), nervous system disorders (5.9% versus 3.6%) and respiratory, thoracic and mediastinal disorders (7.8% versus 2.2%) appears to be higher in the group of adolescents than in adults.

Initially, the MAH proposed for the topical application a general age limitation for children below 12 years based on the established positive benefit/risk in the adult population, the pharmacokinetic data and post-marketing experience in adolescents.

Summary of comments received from MS:

NL did not agree with the treatment of children and adolescents by topical diclofenac at all. UK referred to similar topical products which are licensed for short-term treatment. SE agreed with the proposal of the Rapporteur.

Conclusions

Age limitation

On basis of the available data, a general recommendation for treatment of children from 12 years on with topical diclofenac appears not justified. The age limitations (14 years for flexible-dosed formulations, 16 years for fixed-dosed formulations like e.g. medicated plasters) proposed by the Rapporteur are agreed by the MAH. This conservative approach appears reasonable taking into account that data from clinical trials are not available in this age group (<18 years).

Wording of SmPC

In detail, the following information should be added to section 4.2 and 4.3 of the SmPC as agreed by the MAH:

- Section 4.2:

- Fixed-dose formulations such as medicated plasters:

- Children and adolescents below 16 years:*

- There are insufficient data on efficacy and safety available for children and adolescents below 16 years of age (see also contraindications section 4.3).*

- Flexible-dosed formulations such as creams and gels:

- Children and adolescents below 14 years:*

- There are insufficient data on efficacy and safety available for children and adolescents below 14 years of age (see also contraindications section 4.3).*

- Section 4.3:

- Fixed-dose formulations such as medicated plasters:

- Children and adolescents:*

- The use in children and adolescents aged less than 16 years is contraindicated.*

- Flexible formulations such as creams and gels:

- Children and adolescents:*

- The use in children and adolescents aged less than 14 years is contraindicated.*

Wording of SmPC - Indication

Taking into account the lack of relevant efficacy data and the fact that systemic availability of diclofenac appears to increase with decreasing age, it is considered appropriate by the Rapporteur to recommend only one acute indication which is considered clinically meaningful for this age group and supported by published efficacy and safety data for other NSAIDs. The following indication for children and adolescents is recommended by the Rapporteur and the wording is agreed in principle by the MAH.

For short-term treatment'

Local symptomatic relief of pain in acute strains, sprains or contusions following blunt trauma.

However, Novartis pointed out that the proposed wording is only consistent with the one recently accepted within the national renewal in Germany. Consequently, based on the current divergent wording for this indication in the member states, the full harmonization of paediatric relevant parts of the product information for diclofenac for children and adolescents apparently cannot be achieved for this indication.

In addition to this, the MAH is of the opinion that the indications "soft-tissue rheumatism pain" and "periarthopathy-related pain" which are approved in some MS should be maintained.

However, data for a treatment of more chronic conditions such as soft-tissue rheumatism and periarthopathy-related pain in adolescents or children have not been submitted for topical diclofenac. Since specific data are not available for children and adolescents, these additional indications are not supported by the Rapporteur.

Based on the current divergent licensed indications in the member states and the divergent opinion of the MAH, the full harmonization of paediatric relevant parts of the product information for diclofenac for children apparently cannot be achieved for this issue.

Wording of SmPC - Additional information concerning consultation of a doctor

The MAH agreed to include the following sentences into section 4.2 of the SPC/PIL:

- OTC topical diclofenac products:
 - For fixed-dose formulations such as medicated plasters:
In children aged 16 years and over, if this product is required for more than 7 days for pain relief or if the symptoms worsen, the patient/parents of the adolescent is/are advised to consult a doctor.'
 - For flexible-dosed formulations such as creams and gels:
In children aged 14 years and over, if this product is required for more than 7 days for pain relief or if the symptoms worsen the patient/parents of the adolescent is/are advised to consult a doctor.'
- Topical diclofenac products for prescription:
 - For fixed-dose formulations such as medicated plasters:
In children aged 16 years and over, if the symptoms worsen the patient/parents of the adolescent is/are advised to consult the doctor.'
 - For flexible-dosed formulations such as creams and gels:
In children aged 14 years and over, if the symptoms worsen the patient/parents of the adolescent is/are advised to consult the doctor.'

Wording of SmPC - Additional aspects

With respect to an additional warnings concerning an increased risk for accidental intake (topical formulation) and potential undesirable systemic effects of topical diclofenac

preparations in children, it is agreed to take up these points in the currently ongoing diclofenac PSUR worksharing procedure for reasons of competence.

The following sentence is proposed to be included into section 4.8 of the SPC/PIL, the proposal will be submitted by BfArM to the PSUR worksharing procedure Rapporteur DK:

Systemic absorption of topically applied diclofenac is very low and the resulting diclofenac plasma levels are also very low compared with plasma levels following oral intake of diclofenac. The probability of systemic undesirable effects (such as e.g. gastrointestinal, hepatic or renal disturbances, bronchospasm) is thus very low following topical application compared with the frequency of undesirable effects associated with oral intake of diclofenac. If diclofenac is used on a large area of skin and for a prolonged period, however, undesirable systemic effects may occur.'

II.3 Ophthalmological application

Diclofenac eye drops are licensed for use in adults only . There is no need in the paediatric population. This is also recommended and justified by the rapporteur (see PrPdAR).